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Prescribing practice of newer antiepileptic drugs in pain therapy – a routine data evaluation

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Title:

**Prescribing practice of newer antiepileptic drugs in pain therapy
– a routine data evaluation**

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40 Abstract

41 **Objectives:** What are the prevalence and incidence for pregabalin and gabapentin (P/G) prescriptions?
42 What are the typical areas of application for P/G? Which pain-related diagnoses are available for P/G
43 users? How high is the rate of discontinuation for P/G?

44 **Design:** A secondary data analysis.

45 **Setting:** Primary and secondary care in Germany.

46 **Participants:** Anonymous accounting data of 4 million insured persons from under the statutory
47 health insurance scheme in 2009-2015.

48 **Intervention:** None.

49 **Primary and secondary outcome measures:** None.

50 **Results:** In 2015, 1.6% of insured persons were given a P/G prescription. Among the pain patients
51 with new P/G prescriptions, only 21.7% had a typical neuropathic pain disorder. For the remaining
52 new P/G recipients (78.3%), there was either no diagnosis of neuropathic pain or a diagnosis in which
53 a neuropathic component was conceivable pathophysiologically, but with no evidence for the use of
54 P/G. The rate of discontinuation for P/G was high (85%). Among the patients, who have discontinued
55 medication, 61.1% did not receive one follow-up prescription within two years.

56 **Conclusion:** The results show that P/G is widely used in cases of chronic pain irrespective of
57 neuropathic pain diagnoses. The high rate of discontinuation indicates that the anticipated therapeutic
58 effects are lacking and/or adverse effects occur.

59 **Trial registration:** None.

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3 61 **Strengths and limitations of this study**

- 4 62 • The findings of this study are based on a routine data evaluation which was carried out for the
5 63 accounting of services. This can lead to systematic restrictions.
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7 64 • Due to following reasons, the pain-related indications may have been insufficiently coded in
8 65 individual cases, e.g. mistakes in the daily routine, clear neuropathic diagnoses may have been
9 66 specifically identified to justify a prescription.
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11 67 • The diagnosis coding of unspecific low back pain were often routinely coded as
12 68 "lumboischialgia" or unspecific neck pain as "cervical neuralgia". This systematic
13 69 misclassification tend towards overestimation of neuropathic diagnosis.
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1. Introduction

The active ingredient pregabalin and gabapentin, hereinafter referred to as pregabalin/gabapentin or P/G, belong to the group of "newer antiepileptic drugs", which were developed for the treatment of epilepsy. Pregabalin/gabapentin was also later approved for the treatment of neuropathic pain (gabapentin: 2001; pregabalin: 2004), which is now the main indication for these active ingredients [1].

Controlled randomised studies showed a slight improvement of neuropathic pain disorder in patients treated with pregabalin/gabapentin compared to placebo; the effects are about as great as those of amitriptyline [2–4]. Adverse effects occur significantly more frequently in the P/G intervention group than in the placebo comparison group [5]. The evidence for the rather small therapeutic effects of P/G, which are approved for the treatment of rare medical conditions, contradicts the prescription figures, which have been increasing steadily for years. According to the medication report, a total of 128 million daily doses of pregabalin/gabapentin were prescribed in 2015 [1]. The Lyrica product by Pfizer (pregabalin) was ranked 26th in 2015 on the list of the highest-revenue medicines under patent-protection with net GKV (statutory health insurance) costs of 170.3 million euros [1]. Prescription data from England describe the same trends [6].

The current study presents an analysis of the prescription situation. The following research questions are the main focuses:

- 1.) How high is the **annual prevalence** for the prescription of pregabalin/gabapentin among all insured persons from 2009 to 2015?
- 2.) How high is the **annual incidence** for new prescriptions of pregabalin/gabapentin among all insured persons from 2009 to 2015?
- 3.) What are the **areas of application** (epilepsy/generalised anxiety disorder/pain) for patients with new pregabalin/gabapentin prescriptions from 2009 to 2015?
- 4.) Which **pain-related diagnoses** (neuropathic pain/non-neuropathic pain/mixed pain/no pain) are applicable to patients without epilepsy diagnosis with new pregabalin/gabapentin prescriptions in 2015?
- 5.) What is the **proportion** of patients for whom pregabalin/gabapentin was discontinued within two years after a new prescription for the treatment of pain?
 - How many follow-up prescriptions were given to patients for whom pregabalin/gabapentin was discontinued?

103 2. Methods

104 2.1. Study design and database

105 The research questions were analysed in a cross-sectional design. The research database of the InGef –
106 Institute for Applied Health Research was used as the data basis for this project. The InGef research
107 database (formerly HRI Research Database) contains accounting data on the utilisation and resource
108 consumption of approx. 6.7 million anonymous insured persons from around 65 health insurance
109 funds and company health insurance funds [7]. The present analysis was based on a sample of almost
110 4 million random samples from the research database, which closely represents the age and gender
111 structure of Germany for the year 2013 (according to Destatis – Federal Statistical Office –
112 31.12.2013). The random sampling enables a longitudinal analysis of insured persons over the years
113 2009-2015; in addition to sociodemographic data, it contains information on medicines prescribed by
114 doctors and dispensed by pharmacies in the form of central pharma numbers (PZN) and ATC codes,
115 ICD diagnoses from outpatient and inpatient areas as well as invoiced medical services.
116 The diagnoses and prescriptions can be linked to the anonymous insured person's name at the end of
117 each quarter.

119 2.2. Random sample analysis

120 The inclusion criteria, which vary according to the question, are presented below (for insured persons
121 who meet the following criteria):

123 **Sample 1** (Question 1 – ANNUAL PREVALENCE):

- 124 • insured for at least one day in the first quarter of the respective reporting year

126 **Sample 2** (Question 2 – ANNUAL INCIDENCE):

- 127 • insured for at least one day in the first quarter of the respective reporting year
- 128 • insured for 365 days in the previous year

130 **Sample 3** (Question 3 – AREAS OF APPLICATION FOR NEW PRESCRIPTION):

- 131 • insured for at least one day in the first quarter of the respective reporting year
- 132 • insured for 365 days in the previous year
- 133 • at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16) in the
134 reporting year, but not in the four previous quarters

136 **Sample 4** (Question 4 – PAIN DIAGNOSES IN THE NEW PRESCRIPTION):

- 137 • insured for at least one day in the first quarter of 2015

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3 138 • no coded epilepsy diagnosis (G40.- | G41.-) in the years 2014-2015
4 139 • no prescription of antiepileptic medication (all N03 codes) in 2014
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6 140 • at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16) in 2015
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9 142 **Sample 5** (Question 5 – DISCONTINUATION):

- 10 143 • insured for at least one day in the first quarter of 2013
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12 144 • no coded epilepsy diagnosis (G40.- | G41.-) in the years 2011-2013
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14 145 • no prescription of antiepileptic medication (all N03 codes) in the years 2011-2012
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16 146 • at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16), and in the
17 same quarter of the prescription, at least one pain diagnosis in 2013
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20 149 2.3 Data evaluation

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22 150 The annual prevalence was calculated individually for each reporting year from 2009 to 2015. All
23 151 insured persons who received at least one P/G prescription (ATC code: N03AX12 or N03AX16)
24 152 within one year were divided by the total number of all insured persons from sample 1 of the
25 153 respective reporting year.
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29 155 The annual incidence was calculated individually for each year from 2010 to 2015 (except for the first
30 156 reporting year: 2009, as no new prescriptions could be identified due to missing data for the previous
31 157 year). To this end, all insured persons who received a pregabalin/gabapentin prescription (ATC code:
32 158 N03AX12 or N03AX16) within one year, but not in the previous year, were compared to the total
33 159 number of all patients from sample 2 of the respective reporting year.
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37 161 The areas of application approved for P/G were analysed individually for each possible combination of
38 162 the diagnoses "Epilepsy (G40.- | G41.-)", "Generalised anxiety disorder (F41.1)" and "Pain (for
39 163 selection of ICD-10 codes, see all pain diagnoses in the last row of Table 1)".
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44 Table 1: **Pain-related diagnoses** in patients with new pregabalin/gabapentin prescriptions in
45 2015 (n=25,251)

Pain-related diagnoses		Number of insured persons	As a percentage
1	Non-neuropathic pain * (exclusive)	2,951	11.7
2	Typical neuropathic pain disorder ** (exclusive) (demonstrable benefit of a P/G therapy)	1,218	4.8
3	Pain with possible neuropathic or partial-neuropathic cause *** (exclusive) (no demonstrable benefit of P/G)	3,025	12.0

1 and 2	1,295	5.1
1 and 3	10,756	42.6
2 and 3	1,010	4.0
1 and 2 and 3	2,990	11.8
neither 1, 2 nor 3	2,006	7.9
<p>Typical neuropathic pain disorder</p> <p>* ICD-10 pain code “not neuropathic”:</p> <p>R522 Other chronic pain M545 Low back pain F4541 Chronic pain disorder related to somatic and psychological factors R51 Headache R529 Pain, unspecified R104 Other and unspecified abdominal pain R103 Pain localised in other parts of lower abdomen R521 Chronic intractable pain M5499 Back pain, unspecified: Localisation not specified in more detail R101 Pain localised in upper abdomen R074 Chest pain, not specified in more detail M2556 Pain in joint: Lower leg [fibula, tibia, knee joint] M7969 Pain in extremities: Localisation not specified in more detail G442 Tension-type headache M2559 Pain in joint: Localisation not specified in more detail F4540 Persistent somatoform pain disorder M546 Pain in area of thoracic spine M2555 Pain in joint: Pelvic region and thigh [pelvis, femur, buttocks, hip, hip joint, sacroiliac joint] M7967 Pain in the extremities: Ankle and foot [tarsal, metatarsal, toes, ankle, joints of the foot] R520 Acute pain M2551 Pain in joint: Shoulder region [clavicle, scapula, acromioclavicular/shoulder/sternoclavicular joints] I7022 Atherosclerosis of arteries of extremities: Pelvic-leg type, with rest pain M2550 Pain in joint: Multiple sites I7021 Atherosclerosis of arteries of extremities: Pelvic-leg type, with load-induced ischaemic pain</p> <p>** ICD-10 pain codes “typically neuropathic”:</p> <p>G629 Polyneuropathy, not specified in more detail B029 Zoster without complication G632 Diabetic polyneuropathy B022 Zoster with involvement of other parts of the nervous system G530 Post-Zoster neuralgia G500 Trigeminal neuralgia G6288 Other specified polyneuropathies</p> <p>*** ICD-10 pain code “possibly neuropathic”:</p> <p>M544 Lumbago with sciatica M5416 Radiculopathy: Lumbar region M542 Cervicalgia M511 Lumbar and other intervertebral disc disorders with radiculopathy G560 Carpal tunnel syndrome M5419 Radiculopathy: Localisation not specified in more detail M5412 Radiculopathy: Cervical region M5417 Radiculopathy: Lumbosacral region M5414 Radiculopathy: Thoracic region M543 Sciatica M501 Cervical disc disorder with radiculopathy M5410 Radiculopathy: Multiple sites in spine G573 Lesion of lateral popliteal nerve M961 Postlaminectomy syndrome, not elsewhere classified G580 Intercostal neuropathy G562 Lesion of ulnar nerve</p>		

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166 In addition, insured persons in Sample 3, to whom one of the above-mentioned diagnosis groups was
167 assigned in parallel to the P/G prescription within a quarter, were divided by all insured persons in
168 Sample 3. These calculations were made individually for each reporting year from 2010 to 2015.

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3 170 To answer the question of which pain-related diagnoses P/G was newly prescribed, the percentage
4 171 distribution of all coded ICD-10 pain diagnoses of the insured persons from sample 4 was presented
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6 172 first. Furthermore, the diagnoses were classified into the three categories "**non-neuropathic** pain", "
7 173 **typical neuropathic** pain disorders for which there is a demonstrable **benefit of a P/G therapy**" and
8
9 174 "pain, **possibly** of **neuropathic** or partial-neuropathic cause for which there is **no demonstrable**
10 175 **benefit of P/G**" [1–4]. The ICD-10 diagnosis classification is presented in the last line of Table 1.
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13 177 The calculation of the number of follow-up prescriptions/rate of discontinuation according to new P/G
14 178 prescriptions was based on sample 5 and relates to the year 2013 plus two years of follow-up
15 179 observation period (up to max. 2015). If in the two-year follow-up period no P/G prescription occurred
16 180 for at least two consecutive quarters, this was defined as a discontinuation of therapy. The percentage
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18 181 of insured persons who discontinued therapy and the number of individual prescriptions up to
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20 182 termination were presented.
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183 3. Results

184 3.1. Prevalence and incidence for P/G prescriptions

185 From 2009-2015, 1.3% (52,774/3,948,482) of insured persons were prescribed at least one P/G
 186 prescription. The prevalence of prescriptions increased from 1.1% in 2009 to 1.6% per annum in 2015
 187 (Table 2a).
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Table 2a: Annual prevalence for pregabalin/gabapentin prescriptions 2009-2015			
Year	Number of insured persons with P/G prescriptions	Number of total insured persons	Prevalence per 100,000 insured persons
2009	41,083	3,822,333	1,074.8
2010	46,225	3,890,247	1,188.2
2011	50,230	4,027,591	1,247.1
2012	53,389	4,019,944	1,328.1
2013	56,358	4,010,383	1,405.3
2014	60,306	3,998,004	1,508.4
2015	61,828	3,870,869	1,597.3
Mean value 2009-2015	52,774	3,948,482	1,335.6

Table 2b: Prevalence for pregabalin/gabapentin prescriptions grouped by age and stratified by gender in 2015			
Age group	Total prevalence per 100,000 insured persons	Prevalence per 100,000 insured women	Prevalence per 100,000 insured men
0-17	13.4	17.5	9.6
18-35	249.2	289.4	210.0
36-55	1,042.5	1,213.2	874.9
56-75	2,899.6	3,146.0	2,634.9
76+	5,302.1	5,709.5	4,658.1
Total	1,597.3	1,869.7	1,312.8
Total 18+	1,894.0	2,197.1	1,571.7

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 190 The prescription rate was highest in the 76+ age group (5,302 persons per 100,000 insured persons in
 191 2015) (Table 2b). The prescription for minors, on the other hand, at 13.4 per 100,000 insured persons,
 192 was low. Compared to men, women were prescribed P/G more frequently (women: a total of 1,869.7
 193 per 100,000 insured persons; men: a total of 1,312.8 per 100,000 insured persons). Like prescription
 194 prevalence, the rate of new P/G prescription increased annually (Table 3).

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Year	Number of insured persons with new P/G prescriptions	Number of total insured persons	Incidence per 100,000 insured persons
2010	22,776	3,701,696	615.3
2011	23,121	3,717,582	621.9
2012	24,750	3,977,347	622.3
2013	25,784	3,966,813	650.0
2014	27,613	3,952,306	698.7
2015	26,526	3,757,502	705.9
Mean value 2010-2015	25,095	3,845,541	652.4

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196 One exception was the last year accounted for, 2015. This showed a slight drop in incidence.

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198 **3.2. Area of application**

199 Considering the three applications approved for P/G, it was found that the majority (77.9%) of P/G
200 recipients had only a pain diagnosis and there was no evidence of epilepsy or anxiety disorder (Table
201 4).

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ICD diagnoses	Number of insured persons with P/G prescriptions	As a percentage
Pain * (exclusive)	48,190	77.9
Epilepsy ** (exclusive)	793	1.3
Anxiety disorder *** (exclusive)	707	1.1
Pain + anxiety disorder	2,404	3.9
Pain + epilepsy	2,222	3.6
Pain + epilepsy + anxiety disorder	162	0.3
Epilepsy + anxiety disorder	49	0.1
No pain, epilepsy or anxiety disorder	7,198	11.6
* all ICD-10 pain diagnoses listed in Table 4 (last row)		
** ICD codes: G40.- G41.-		
*** ICD codes: F41.1		

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204 There was no evidence for the approved application diagnoses according to Fachinfo for 11.6% of the
205 P/G recipients. P/G recipients exclusively with a diagnosis of epilepsy or anxiety (epilepsy: 1.3%;

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3 206 anxiety 1.1%) were the minority. The percentage of new P/G recipients (excluding pain diagnoses)
4 207 increased continuously over the years. The proportion of existing epilepsy and anxiety diagnoses
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6 208 remained relatively constant in the new P/G prescriptions group.
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9 210 **3.3. Application in pain patients**

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11 211 After excluding epilepsy patients, 25,251 insured persons remained under new P/G prescription,
12 212 whose pain diagnoses were analysed. A typical neuropathic pain disorder was present in one fifth of
13 213 all new P/G recipients (21.7%), Table 1. For the majority (58.6%) of new recipients, a diagnosis was
14 214 made in which a neuropathic component was conceivable pathophysiologically, but with no evidence
15 215 for the use of P/G. The three most frequent representatives in this category were the diagnoses
16 216 "M544_Lumboischialgia" (5,836/25,251), "M5416_Radiculopathy: Lumbar region" (4,978/25,251)
17 217 and "M542_Cervical neuralgia" (4,543/25,251). In 19.6% of the cases, there was only a "non-
18 218 neuropathic pain diagnosis" or "no pain diagnosis".
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24 220 **3.4. Discontinuation**

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26 221 Within the follow-up period, 85% (16,573/19,501) of insured persons who received a new P/G
27 222 prescription due to pain (excluding patients with epilepsy diagnosis) were again discontinued within
28 223 two years. For the majority of the persons, who have discontinued, the discontinuation occurred within
29 224 a short period. Thus, in 61.1% of the cases, there was no follow-up prescription after the initial
30 225 prescription (number of follow-up-prescriptions / proportion in percent: 1/13.2%; 2/7.5%; 3/5.4%;
31 226 $\geq 4/12.8\%$). The proportion of P/G insured persons with regular follow-up prescriptions over the
32 227 follow-up period was 15% (2,928/19,501).
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228 4. Discussion

229 The prescription figures for pregabalin and gabapentin increased annually from 2009 to 2015. The
230 majority of patients (78%) received P/G for the treatment of pain. In patients who received new P/G
231 prescriptions, only about one in five (22%) had a typical neuropathic pain disorder with a
232 demonstrable benefit of a P/G therapy. For the remaining new P/G recipients (78.3%), there was either
233 no diagnosis of neuropathic pain or a diagnosis in which a neuropathic component was conceivable
234 pathophysiologically, but with no evidence for the use of P/G. The rate of discontinuation for P/G was
235 high; based on new prescriptions, 51.9% of cases did not receive a follow-up prescription within two
236 years.

237
238 The findings of this study are based on a routine data evaluation, which was carried out independently
239 of the research questions, specifically for the accounting of services in the daily treatment routine. This
240 can lead to systematic restrictions [8]. Regarding the information relevant to this project "P/G
241 consumption", a typical realistic representation can be assumed due to the prescription requirement for
242 P/G-containing medicinal products. However, the pain-related indications may have been
243 insufficiently coded in individual cases. For example, clear neuropathic diagnoses may have been
244 specifically identified to justify a prescription. Presumably, the proportion of evidence-based
245 indications is even lower in reality. In the diagnosis coding of unspecific low back pain as well,
246 systematic misclassifications that tend towards overestimation are likely, since they are often routinely
247 coded as "lumboischialgia" or unspecific neck pain as "cervical neuralgia".

248
249 The increase in the number of P/G prescriptions found in this analysis coincides with figures from the
250 IMS health database from the United Kingdom [6]. The steadily increasing number of prescriptions
251 with a constant incidence of purely neuropathic pain disorders indicates that P/G is increasingly being
252 used in patients with "mixed chronic pain ("mixed pain")". This observation has also made by
253 Goodman et al. in an issue of the New England Journal of Medicine in August 2017 [6]. "Mixed pain"
254 refers to chronic pain syndromes in which a mixture of nociceptive and neuropathic pain components
255 is assumed. Instruments specially developed for this purpose, such as the painDETECT questionnaire,
256 are designed to identify the neuropathic pain component [9] and are promoted accordingly. However,
257 the pre-approval P/G studies only included patients with pure neuropathic pain as a result of damage to
258 somatosensory nerve structures, e.g. with post-zoster neuralgia or diabetic polyneuropathy. High-
259 quality qualitative studies on the efficacy of P/G in patients with mixed chronic pain are not yet
260 available [10]. In the current edition of the guideline "Non-specific low back pain", the NVL guideline
261 group also opposes a screening using painDETECT [11] due to a lack of evidence.

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263 In consideration of the pain diagnoses, which are coded in parallel to new P/G prescriptions, the
264 question arises as to which diagnoses should be classified as neuropathic or non-neuropathic.

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3 265 In the S1 guideline "Diagnostics of neuropathic pain" [12] of the German Society of Neurology, for
4 266 example, in addition to the pure neuropathic pain syndromes with damage to somatosensory nerve
5 267 structures, pain diagnoses in which a neuropathic component is pathophysiologically conceivable,
6 268 such as "lumboischialgia" or "radiculopathy", are classified as neuropathic. The pain of these
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8 269 conditions is typically caused by nerve irritation, but this does not necessarily constitute damage. In
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10 270 these cases, there is often no evidence of benefit for the application of P/G. In this regard, an RCT
11 271 published in March 2017 by Mathieson et al. showed the non-benefit of pregabalin [13]. Within the
12 272 scope of this project, we decided to differentiate between "typical neuropathic pain disorder" with a
13 273 demonstrable benefit of P/G therapy and "pain, possibly with neuropathic or partially-neuropathic
14 274 cause" with no evidence for the application of P/G. Subsequently, a typical neuropathic pain disorder
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16 275 is presented exclusively in one fifth of the new P/G prescriptions. This phenomenon is increasingly
17 276 being described and critically discussed internationally [6, 14]. Abroad, there is also an increasing
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19 277 reference to the fact that P/G is also abused by addicts as a drug booster [15, 16].
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23 279 The high discontinuation rate suggests two causes. On the one hand, the hoped-for pain-relieving
24 280 effect is not achieved, and on the other hand the therapy is discontinued due to adverse effects.
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26 281 Ultimately, P/G was prescribed as a long-term therapy only for a small minority. This is thought to be
27 282 the typical neuropathic pain cases in which P/G has been shown to have an effect. In all other cases,
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29 283 the discontinued therapy trial underlines that the widely practised and promoted strategy of using P/G
30 284 also in mixed chronic pain patients is not useful. The cause of pain in these cases is multifactorial and
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32 285 usually cannot be solved by medicine.
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35 287 In view of the discrepancy between the high number of prescriptions and the discontinuation rate, as
36 288 an indirect parameter of a clinically unconvincing effect, the question arises as to the motives for the
37 289 high number of prescriptions. The marketing by the pharmaceutical industry [6], among others, which
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39 290 was specifically targeted at the treatment of mixed-pain patients with neuropathic symptoms, may play
40 291 an important role. The influence of pharmaceutical marketing may also be an explanation for the slight
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42 292 drop in the incidence of new prescriptions in 2015. Pregabalin generics were introduced in December
43 293 2014, which could have led to a possible withdrawal of marketing efforts by the patent-holding
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45 294 company.

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47 295 A further motive for doctors to prescribe it may be the one-sided biomedical understanding of chronic
48 296 pain, out of which pain symptoms are too often answered with the prescription of a painkiller rather
49 297 than with non-medicinal measures or counselling. Furthermore, there is no convincing therapeutic
50 298 approach for the effective treatment of chronic pain patients to date. Multimodal therapy programmes
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52 299 are not sufficiently available and, in their current inpatient or short-term outpatient configuration, do
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54 300 not solve the problems of the continuous care situation in established practices. Frustration among
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3 301 both doctors and patients may trigger desperate measures such as the use of newer antiepileptic
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3 303 **5. Study protocol**
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5 304 The study protocol is available on request. Please contact: annika.viniol@staff.uni-marburg.de.
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9 306 This research received no specific grant from any funding agency in the public, commercial or not-for-
10 profit sectors.
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13 308 **7. Competing interests**
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15 309 The authors declare that they have no competing interests.
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18 310 **9. Authors' contributions**
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20 311 AV planned the study, discussed the results and wrote the manuscript. TP and LH analyzed data and
21 discussed the manuscript. KMK gave support to study design and discussed the manuscript. JW, JH,
22 NDB and AB discussed the results and the manuscript.
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26 314 **10. Reporting statement**
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28 315 Data analysis and reporting style is in accordance with the “German Reporting Standard for Secondary
29 Data Analyses” (STROSA).
30 316

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32 317 **11. Patient consent**
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34 318 Due to the nature of secondary data analysis, no patient consent is required.
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38 319 **12. Data sharing statement**
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40 320 Data used in the analyses are entrusted in the Institute for Applied Health Research Berlin. Please
41 contact: jochen.walker@hrisk.de
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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5-8
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	Cross sectional study
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-8
Bias	9	Describe any efforts to address potential sources of bias	5-8
Study size	10	Explain how the study size was arrived at	Secondary data analysis
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Cross sectional study
		(b) Describe any methods used to examine subgroups and interactions	5-8
		(c) Explain how missing data were addressed	5-8
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	5-8

		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	
			Cross sectional study
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9-11 Secondary data analysis Secondary data analysis
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	9-11 9-11 Cross sectional study
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	Cross sectional study Cross sectional study 9-11
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Cross sectional study 9-11 9-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Cross sectional study
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13-14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Title:

**Prescribing practice of pregabalin / gabapentin in pain therapy
– an evaluation of German claim data**

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40 Abstract

41 **Objectives:** To describe the prevalence and incidence of pregabalin and gabapentin (P/G)
42 prescriptions, typical therapeutic uses of P/G with careful attention to pain-related diagnoses, and
43 discontinuation rates of P/G.

44 **Design:** A secondary data analysis.

45 **Setting:** Primary and secondary care in Germany.

46 **Participants:** Anonymous health insurance data of 4 million insured persons in the space of time from
47 2009 to 2015.

48 **Intervention:** None.

49 **Primary and secondary outcome measures:** We analysed the prescribing practice of P/G in general
50 and investigate the use of P/G in pain therapy. We focused on the question due to which pain-related
51 diagnoses patients get a new P/G prescription and illustrated the discontinuation rate of P/G.

52 **Results:** In 2015, 1.6% of insured persons were given a P/G prescription. Among the pain patients
53 with new P/G prescriptions, only 25.7% had a typical neuropathic pain disorder. For the remaining
54 new P/G recipients (74.3%), there was either no diagnosis of neuropathic pain or a diagnosis in which
55 a neuropathic component was conceivable pathophysiologically, but with no evidence for the use of
56 P/G. The rate of discontinuation for P/G was high (85%). Among the patients who had discontinued
57 medication, 61.1% did not receive one follow-up prescription within two years.

58 **Conclusion:** The results show that P/G is widely used in cases of chronic pain irrespective of
59 neuropathic pain diagnoses. The high rate of discontinuation indicates that the anticipated therapeutic
60 effects are lacking and/or adverse effects occur.

61 **Trial registration:** None.

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3 **62 Strengths and limitations of this study**

- 4 63 • The findings of this study are based on accounting data on the utilisation and resource
5 consumption of insured persons from health insurance funds. These secondary data can lead to
6 64 systematic restrictions.
7 65
8 66 • The pain-related indications may have been insufficiently coded (documentation errors)
9
10 67 • The diagnosis coding of unspecific low back pain were often routinely coded as
11 "lumboischialgia" or unspecific neck pain as "cervical neuralgia". This systematic
12 68 misclassification tend towards overestimation of neuropathic diagnosis.
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1. Introduction

The active ingredient pregabalin and gabapentin, hereinafter referred to as pregabalin/gabapentin or P/G, belong to the group of "newer antiepileptic drugs", which were developed for the treatment of epilepsy. The European Medicines Agency approved Pregabalin/gabapentin also later for the treatment of neuropathic pain (Pregabalin (2004): "peripheral and central neuropathic pain"; Gabapentin (2001): "peripheral neuropathic pain like painful diabetic neuropathy and post herpetic neuralgia" [1]), which is now a common indication for these active ingredients [2].

Controlled randomised studies showed a slight improvement of specific forms of neuropathic pain disorder in patients treated with pregabalin/gabapentin compared to placebo [3–5]. The evidence for the rather small therapeutic effects of P/G, which are approved for the treatment of a rather minor condition spectrum, contradicts the prescription figures, which have been increasing steadily for years. According to the medication report, a total of 128 million daily doses of pregabalin/gabapentin were prescribed in 2015 [2]. The Lyrica product by Pfizer (pregabalin) was ranked 26th in 2015 on the list of the highest-revenue medicines under patent-protection with net GKV (statutory health insurance) costs of 170.3 million euros [2]. US Prescription data describe the same trends. The gabapentin prescription rate has been raised from 39 million in 2012 to 64 million in 2016 in the United States [6, 7].

The above described increasing P/G prescribing makes us concerned, why we investigate the prescribing practice in this study. The following research questions are the main focuses:

- 1.) How high is the **annual prevalence** for the prescription of pregabalin/gabapentin among all insured persons from 2009 to 2015?
- 2.) How high is the **annual incidence** for new prescriptions of pregabalin/gabapentin among all insured persons from 2009 to 2015?
- 3.) What are the **indications for prescribing** (epilepsy/generalised anxiety disorder/pain) for patients with new pregabalin/gabapentin prescriptions from 2009 to 2015?
- 4.) Which **pain-related diagnoses** (neuropathic pain/non-neuropathic pain/mixed pain/no pain) are applicable to patients without epilepsy diagnosis with new pregabalin/gabapentin prescriptions in 2015?
- 5.) What is the **proportion** of patients for whom pregabalin/gabapentin was discontinued within two years after a new prescription for the treatment of pain?
 - How many follow-up prescriptions were given to patients for whom pregabalin/gabapentin was discontinued?

103 2. Methods

104 2.1. Study design and database

105 The research questions were analysed in a cross-sectional design. The research database of the InGef –
106 Institute for Applied Health Research was used as the data basis for this project. The InGef research
107 database (formerly HRI Research Database) contains data on the utilisation and resource consumption
108 of approx. 6.7 million anonymous insured persons from around 65 health insurance funds and
109 company health insurance funds [8]. As long as the insured persons are members of these health
110 insurances, their data are all-encompassing available in this database and were no competing to other
111 databases. When insurant change to another insurance which is not linked with this database, their data
112 are still not available in this database. The present analysis was based on a sample of almost 4 million
113 random samples from the research database, which closely represents the age and gender structure of
114 Germany for the year 2013 (according to Destatis – Federal Statistical Office – 31.12.2013). The
115 random sampling enables a longitudinal analysis of insured persons over the years 2009-2015; in
116 addition to sociodemographic data, it contains information on medicines prescribed by doctors and
117 dispensed by pharmacies in the form of central pharma numbers (PZN) and ATC codes, ICD
118 diagnoses from outpatient and inpatient areas as well as invoiced medical services.
119 The diagnoses and prescriptions can be linked to the anonymous insured person's name at the end of
120 each quarter. In every analysis, all dosage forms and formulations of P/G were included.

122 2.2. Random sample analysis

123 The inclusion criteria, which vary according to the question, are presented below (for insured persons
124 who meet the following criteria):

126 **Sample 1** (Question 1 – ANNUAL PREVALENCE):

127 Persons who were insured for at least one day in the first quarter of the respective reporting year.

129 **Sample 2** (Question 2 – ANNUAL INCIDENCE):

130 Persons who were insured for at least one day in the first quarter of the respective reporting year and
131 365 days in the previous year.

133 **Sample 3** (Question 3 – INDICATIONS FOR PRESCRIBING FOR NEW PRESCRIPTION):

134 Persons who were insured for at least one day in the first quarter of the respective reporting year and
135 365 days in the previous year with at least one pregabalin/gabapentin prescription (ATC code:
136 N03AX12 or N03AX16) in the reporting year, but not in the four previous quarters (independent from
137 diagnosis).

138

139 **Sample 4** (Question 4 – PAIN DIAGNOSES IN THE NEW PRESCRIPTION):

140 Persons who were insured for at least one day in the first quarter of 2015 and fulfil the following
141 criteria: no coded epilepsy diagnosis (G40.- | G41.-) in the years 2014-2015; no prescription of
142 antiepileptic medication (all N03 codes) in 2014; at least one pregabalin/gabapentin prescription (ATC
143 code: N03AX12 or N03AX16) in 2015

144

145 **Sample 5** (Question 5 – DISCONTINUATION):

146 Persons who were insured for at least one day in the first quarter of 2013 and fulfil the following
147 criteria: no coded epilepsy diagnosis (G40.- | G41.-) in the years 2011-2013; no prescription of
148 antiepileptic medication (all N03 codes) in the years 2011-2012; at least one pregabalin/gabapentin
149 prescription (ATC code: N03AX12 or N03AX16), and in the same quarter of the prescription, at least
150 one pain diagnosis in 2013

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152 **2.3 Data evaluation**

153 The annual prevalence was calculated individually for each reporting year from 2009 to 2015. All
154 insured persons who received at least one P/G prescription (ATC code: N03AX12 or N03AX16)
155 within one year were divided by the total number of all insured persons from sample 1 of the
156 respective reporting year.

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158 The annual incidence was calculated individually for each year from 2010 to 2015 (except for the first
159 reporting year: 2009, as no new prescriptions could be identified due to missing data for the previous
160 year). To this end, all insured persons who received a pregabalin/gabapentin prescription (ATC code:
161 N03AX12 or N03AX16) within one year, but not in the previous year, were compared to the total
162 number of all patients from sample 2 of the respective reporting year.

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164 The areas of indications for P/G prescribing were analysed individually for each possible combination
165 of the diagnoses "Epilepsy (G40.- | G41.-)", "Generalised anxiety disorder (F41.1)" and "Pain (all ICD-
166 codes including the term "pain")". The used pain related ICDs are illustrated in the supplementary
167 material. In addition, insured persons in Sample 3, to whom one of the above-mentioned diagnosis
168 groups was assigned in parallel to the P/G prescription within a quarter, were divided by all insured
169 persons in Sample 3. These calculations were made individually for each reporting year from 2010 to
170 2015.

171

172 To answer the question of which pain-related diagnoses P/G was newly prescribed, the percentage
173 distribution of all coded ICD-10 pain diagnoses of the insured persons from sample 4 was presented
174 first. Furthermore, the diagnoses were classified into the following three categories: Diagnoses with an

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3 175 improved evidence (via controlled randomised studies) for P/G were classified as "**typical**
4 176 **neuropathic pain** disorders for which there is a demonstrable **benefit of a P/G** therapy" [2–5].
5
6 177 Diseases with a potentially neuropathic genesis based upon aetiology/anatomical deliberations,
7 178 independent from the therapeutic benefit of P/G [9] were classified as "pain, **possibly of neuropathic**
8 179 or partial-neuropathic cause for which there is **no demonstrable benefit of P/G**". All other pain
9
10 180 diagnose, were labelled as "**non-neuropathic** pain". The ICD-10 diagnosis classification is presented
11 181 as supplementary data.
12
13 182

14 183 The calculation of the number of follow-up prescriptions/rate of discontinuation according to new P/G
15 184 prescriptions was based on sample 5 and relates to the year 2013 plus two years of follow-up
16 185 observation period (up to max. 2015). If in the two-year follow-up period no P/G prescription occurred
17 186 for at least two consecutive quarters, this was defined as a discontinuation of therapy. The percentage
18 187 of insured persons who discontinued therapy and the number of individual prescriptions up to
19 188 termination were presented.
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24 25 190 **2.4 Patient and Public Involvement**

26
27 191 This work focusses on the prescribing practice of P/G in pain therapy, which enable a critical
28 192 reflection of this drugs and probably prevent over- and/or undertreatment. This secondary data
29 193 analysis does not involve individuals. We did no recruitment. Patients were not involved in the study
30 194 development. Beside this publication, we present the data of this analysis on conferences.
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195 **3. Results**

196 **3.1. Prevalence and incidence for P/G prescriptions**

197 From 2009-2015, 1.3% (52,774/3,948,482) of insured persons were prescribed at least one P/G
 198 prescription. The prevalence of prescriptions increased from 1.1% in 2009 to 1.6% per annum in 2015
 199 (Table 1a).
 200

Table 1a: **Annual prevalence** for pregabalin/gabapentin prescriptions 2009-2015

Year	Number of insured persons with P/G prescriptions	Number of total insured persons	Prevalence per 100,000 insured persons
2009	41,083	3,822,333	1,074.8
2010	46,225	3,890,247	1,188.2
2011	50,230	4,027,591	1,247.1
2012	53,389	4,019,944	1,328.1
2013	56,358	4,010,383	1,405.3
2014	60,306	3,998,004	1,508.4
2015	61,828	3,870,869	1,597.3
Mean value 2009-2015	52,774	3,948,482	1,335.6

Table 1b: **Prevalence** for pregabalin/gabapentin prescriptions grouped by age and stratified by gender in 2015

Age group	Total prevalence per 100,000 insured persons	Prevalence per 100,000 insured women	Prevalence per 100,000 insured men
0-17	13.4	17.5	9.6
18-35	249.2	289.4	210.0
36-55	1,042.5	1,213.2	874.9
56-75	2,899.6	3,146.0	2,634.9
76+	5,302.1	5,709.5	4,658.1
Total	1,597.3	1,869.7	1,312.8
Total 18+	1,894.0	2,197.1	1,571.7

201

202 The prescription rate was highest in the 76+ age group (5,302 persons per 100,000 insured persons in
 203 2015) (Table 1b). The prescription for minors, on the other hand, at 13.4 per 100,000 insured persons,
 204 was low. Compared to men, women were prescribed P/G more frequently (women: a total of 1,869.7
 205 per 100,000 insured persons; men: a total of 1,312.8 per 100,000 insured persons). Like prescription
 206 prevalence, the rate of new P/G prescription increased annually (Table 2).

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Year	Number of insured persons with new P/G prescriptions	Number of total insured persons	Incidence per 100,000 insured persons
2010	22,776	3,701,696	615.3
2011	23,121	3,717,582	621.9
2012	24,750	3,977,347	622.3
2013	25,784	3,966,813	650.0
2014	27,613	3,952,306	698.7
2015	26,526	3,757,502	705.9
Mean value 2010-2015	25,095	3,845,541	652.4

207

208 3.2. Area of application

209 Considering the three applications approved for P/G, it was found that the majority (77.9%) of P/G
210 recipients had only a pain diagnosis and there was no evidence of epilepsy or anxiety disorder (Table
211 3).

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ICD diagnoses	Number of insured persons with P/G prescriptions	As a percentage
Pain * (exclusive)	48,190	77.9
Epilepsy ** (exclusive)	793	1.3
Anxiety disorder *** (exclusive)	707	1.1
Pain + anxiety disorder	2,404	3.9
Pain + epilepsy	2,222	3.6
Pain + epilepsy + anxiety disorder	162	0.3
Epilepsy + anxiety disorder	49	0.1
No pain, epilepsy or anxiety disorder	7,198	11.6
* all ICD-10 pain diagnoses listed in the supplementary information		
** ICD codes: G40.- G41.-		
*** ICD codes: F41.1		

213

214 There was no evidence for the approved application diagnoses for 11.6% of the P/G recipients. P/G
215 recipients exclusively with a diagnosis of epilepsy or anxiety (epilepsy: 1.3%; anxiety 1.1%) were the
216 minority. The percentage of new P/G recipients (excluding pain diagnoses) increased continuously

217 over the years. The proportion of existing epilepsy and anxiety diagnoses remained relatively constant
218 in the new P/G prescriptions group.

219

220 3.3. Application in pain patients

221 After excluding epilepsy patients, 25,251 insured persons remained under new P/G prescription,
222 whose pain diagnoses were analysed. A typical neuropathic pain disorder was present in one quarter of
223 all new P/G recipients (25.7%), Table 4.

224

Table 4: Pain-related diagnoses in patients with new pregabalin/gabapentin prescriptions in 2015 (n=25,251)			
Pain-related diagnoses		Number of insured persons	As a percentage
1	Non-neuropathic pain * (exclusive)	2,951	11.7
2	Typical neuropathic pain disorder ** (exclusive) (demonstrable benefit of a P/G therapy)	1,218	4.8
3	Pain with possible neuropathic or partial-neuropathic cause *** (exclusive) (no demonstrable benefit of P/G)	3,025	12.0
1 and 2		1,295	5.1
1 and 3		10,756	42.6
2 and 3		1,010	4.0
1 and 2 and 3		2,990	11.8
neither 1, 2 nor 3		2,006	7.9

225

226 For the majority (70.4%) of new recipients, a diagnosis was made in which a neuropathic component
227 was conceivable pathophysiologically, but with no evidence for the use of P/G. The three most
228 frequent representatives in this category were the diagnoses "M544_Lumboischialgia"
229 (5,836/25,251), "M5416_Radiculopathy: Lumbar region" (4,978/25,251) and "M542_Cervical
230 neuralgia" (4,543/25,251). In 19.6% of the cases, there was exclusively only a "non-neuropathic pain
231 diagnosis" or "no pain diagnosis".

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233 3.4. Discontinuation

234 Within the follow-up period, 85% (16,573/19,501) of insured persons who received a new P/G
235 prescription due to pain (excluding patients with epilepsy diagnosis) were again discontinued within
236 two years. For the majority of the persons, who have discontinued, the discontinuation occurred within
237 a short period. Thus, in 61.1% of the cases, there was no follow-up prescription after the initial

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3 238 prescription (number of follow-up-prescriptions / proportion in percent: 1/13.2%; 2/7.5%; 3/5.4%;
4 239 $\geq 4/12.8\%$). The proportion of P/G insured persons with regular follow-up prescriptions over the
5
6 240 follow-up period was 15% (2,928/19,501).
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241 4. Discussion

242 The prescription figures for pregabalin and gabapentin increased annually from 2009 to 2015. The
243 majority of patients (78%), who are receiving P/G, have a pain diagnosis. In patients who received
244 new P/G prescriptions, only about one quarter (25.7%) had a typical neuropathic pain disorder with a
245 demonstrable benefit of a P/G therapy. For the remaining new P/G recipients (74.3%), there was either
246 no diagnosis of neuropathic pain or a diagnosis in which a neuropathic component was conceivable
247 pathophysiologically, but with no evidence for the use of P/G. The rate of discontinuation for P/G was
248 high; based on new prescriptions, 51.9% of cases did not receive a follow-up prescription within two
249 years.

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251 The increasing number of P/G prescriptions found in this analysis coincides with data from the IMS
252 health database from the United States [6, 7]. Goodman et al. state in an issue of the New England
253 Journal of Medicine in August 2017, that growth of P/G prescriptions was likely in “chronic non-
254 cancer pain” as an alternative to opiates [7]. The in our work founded, steadily increasing number of
255 prescriptions with a constant incidence of purely neuropathic pain disorders indicates that P/G is
256 increasingly being used in patients with "mixed chronic pain ("mixed pain)". "Mixed pain" refers to
257 chronic pain syndromes in which a mixture of nociceptive and neuropathic pain components is
258 assumed [10, 11]. Instruments specially developed for this purpose, such as the painDETECT
259 questionnaire, are designed to identify the neuropathic pain component [12] and are promoted
260 accordingly. However, the pre-approval P/G studies only included patients with pure neuropathic pain
261 as a result of damage to somatosensory nerve structures, e.g. with post-zoster neuralgia or diabetic
262 polyneuropathy. High-quality qualitative studies on the efficacy of P/G in patients with mixed chronic
263 pain are not yet available [13]. In the current edition of the guideline "Non-specific low back pain", the
264 NVL guideline group also opposes a screening using painDETECT [14] due to a lack of evidence.
265 The increasing prescribing rate among elderly might depend on the fact that chronic pain diagnosis
266 generally increases by age [15].

267
268 In consideration of the pain diagnoses, which are coded in parallel to new P/G prescriptions, the
269 question arises as to which diagnoses should be classified as neuropathic or non-neuropathic.
270 In the S1 guideline "Diagnostics of neuropathic pain" [9] of the German Society of Neurology, for
271 example, in addition to the pure neuropathic pain syndromes with damage to somatosensory nerve
272 structures, pain diagnoses in which a neuropathic component is pathophysiologically conceivable,
273 such as "lumboischialgia" or “radiculopathy”, are classified as neuropathic. The pain of these
274 conditions is typically caused by nerve irritation, but this does not necessarily constitute damage. In
275 these cases, there is often no evidence of benefit for the application of P/G. In this regard, an RCT
276 published in March 2017 by Mathieson et al. showed the non-benefit of pregabalin [16]. Within the
277 scope of this project, we decided to differentiate between "typical neuropathic pain disorder" with a

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3 278 demonstrable benefit of P/G therapy and "pain, possibly with neuropathic or partially-neuropathic
4 279 cause" with no evidence for the application of P/G. Subsequently, a typical neuropathic pain disorder
5 280 is presented exclusively in one fifth of the new P/G prescriptions. This phenomenon is increasingly
6 281 being described and critically discussed internationally [7, 17]. Abroad, there is also an increasing
7 282 reference to the fact that P/G is also abused by addicts as a drug booster [18, 19].
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11 284 The high discontinuation rate suggests three possible causes: First, the pain might be disappeared.
12 285 Second, the hoped-for pain-relieving effect is not achieved. Thirdly, the therapy is discontinued due to
13 286 adverse effects. Ultimately, P/G was prescribed as a long-term therapy only for a small minority. This
14 287 is thought to be the typical neuropathic pain cases in which P/G has been shown to have an effect. In
15 288 all other cases, the discontinued therapy trial underlines that the widely practised and promoted
16 289 strategy of using P/G also in mixed chronic pain patients is not useful. The cause of pain in these cases
17 290 is multifactorial and usually cannot be solved by medicine. Finally, we are not able to perceive the real
18 291 reasons for the high discontinuation rate on the base of this routine data. To answer the question, a
19 292 patient-based survey might be the first choice to investigate this question.
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22 294 The discrepancy between the high number of prescriptions and the discontinuation rate, as a
23 295 potentially indirect parameter of a clinically unconvincing effect, arises the question to the motives for
24 296 the high number of prescriptions. We speculate, that one possible motive for doctors to prescribe it
25 297 may be the one-dimensional biomedical understanding of chronic pain, out of which pain symptoms
26 298 are too often answered with the prescription of a painkiller rather than with non-medicinal measures or
27 299 counselling. Furthermore, there is no convincing therapeutic approach for the effective treatment of
28 300 chronic pain patients to date. Multimodal therapy programmes are not sufficiently available and, in
29 301 their current inpatient or short-term outpatient configuration, do not solve the problems of the
30 302 continuous care situation in established practices. Frustration among both doctors and patients may
31 303 trigger desperate measures such as the use of newer antiepileptic medicine. Furthermore, the
32 304 marketing by the pharmaceutical industry [7], among others, which was specifically targeted at the
33 305 treatment of mixed-pain patients with neuropathic symptoms, may play an important role.
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35 306

36 307 Altogether, the results of this analysis provide an indication of overprescribing of P/G. On the one
37 308 hand, it means that several patients probably take unnecessary drugs going along with the risk of
38 309 polypharmacy, potential side effects and interaction. An on the other hand, it implies a high economic
39 310 burden for the health care system. For example, the costs for pregabalin has been doubled from 2012
40 311 to \$4.4 billion in 2016 in the United States [6, 7]. German data describe the same trends [2]. There are
41 312 possible savings for health insurance funds.
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3 314 The secondary data analysis, which is based on accounting data on the utilisation of insured persons
4 315 from health insurance funds, can lead to systematic restrictions [20]. The variable "P/G consumption"
5 316 can be considered as a valid indicator because P/G is only available on prescription. However, the
6 317 operationalisation of the pain-related diagnosis variables is more challenging due to the fact, that the
7 318 diagnosis coding maybe insufficiently coded in individual cases. One possibility are random errors
8 319 during the diagnosis coding, which result in a potential bias in both directions (more or less than in
9 320 reality). Another possibility may be, that doctors prefer to code clear neuropathic diagnoses to justify
10 321 the prescription even in cases where the neuropathic nature is unclear. This might result in a bias,
11 322 where the proportion of evidence-based indications is even lower in reality. In the diagnosis coding of
12 323 unspecific low back pain as well, systematic misclassifications that tend towards overestimation are
13 324 likely, since they are often routinely coded as "lumboischialgia" / "Radiculopathy: Lumbar region" or
14 325 unspecific neck pain as "cervical neuralgia".

15 326 According to international literature, G/P has also sometimes used in off-label indications like hot
16 327 flush, restless leg, multiple sclerosis [21]. Our methodologically approach, does not account these
17 328 potentially off label indications, which may lead to a bias. Patients would be mistakenly assumed to be
18 329 using P/G for a non-neuropathic pain condition, when in fact they were using it for such an off-label
19 330 indication.

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21 332 Conclusion:

22 333 The results show that chronic pain patients often get pregabalin or gabapentin independent from a
23 334 neuropathic pain diagnose. The high rate of discontinuation indicates that the anticipated therapeutic
24 335 effects are lacking and/or adverse effects occur.

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3 336 **5. Study protocol**
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5 337 The study protocol is available on request. Please contact: annika.viniol@staff.uni-marburg.de.
6

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10 profit sectors.
11 340

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14 341 **7. Competing interests**
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16 342 The authors declare that they have no competing interests.
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19 343 **9. Authors' contributions**
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21 344 AV planned the study, discussed the results and wrote the manuscript. TP and LH analyzed data and
22 discussed the manuscript. KMK gave support to study design and discussed the manuscript. JW, JH,
23 NDB and AB discussed the results and the manuscript.
24 346

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26 347 **10. Reporting statement**
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28 348 Data analysis and reporting style is in accordance with the “German Reporting Standard for Secondary
29 Data Analyses” (STROSA).
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33 350 **11. Patient consent**
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35 351 Due to the nature of secondary data analysis, no patient consent is required.
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37

38 352 **12. Data sharing statement**
39

40 353 Data used in the analyses are entrusted in the Institute for Applied Health Research Berlin. Please
41 contact: jochen.walker@hrisk.de
42 354
43 355

356 **REFERENCES**

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The classification criteria of the pain-related diagnosis

ICD-10 pain code “not neuropathic”

F413	fear/tension- type pain syndrome
F4534	psychogenic painful micturition
F4539	psychogenic pain of the abdomen
F4540	continuing somatoform disorder
F4541	chronic pain with somatic and psychological factors
G440	cluster headache
G441	vasomotor headache
G442	tension headache
G443	chronic posttraumatic headache
G444	headache caused by drugs
G448	other headache without detailed specification
G501	atypical facial pain
H571	eye pain
I702	arteriosclerosis of the extremities: physical stress induced leg pain
L905	cicatix pain
M2550	joint pain: multiple sites
M2551	joint pain: shoulder region (clavícula, scapula, acromioclavicular-/shoulder-/sternoclavicular joints)
M2552	joint pain: upper arm (humerus, elbow joint)
M2553	joint pain: forearm (radius, ulna, wrist)
M2554	joint pain: hand (finger, carpus, metacarpus)
M2555	joint pain: pelvic region and thigh (pelvis, femur, buttocks, hip, hip joint, sacroiliac joint)
M2556	joint pain: lower leg (fibula, tibia, knee joint)
M2557	joint pain: ankle and foot (tarsal, metatarsal, toes, ankle, subtalar joint, other ankle joints)
M2558	joint pain: multiple sites (neck, head, ribs, torso, spine)
M2559	joint pain: multiple localisation
M545	back pain
M546	pain in area of thoracic spine
M5480	other back pain: different areas of the spine
M5481	other back pain: atlanto-occipital joint
M5482	other back pain: cervical area
M5483	other back pain: cervical-thoracic area
M5484	other back pain: thoracic area
M5485	other back pain: thoracic-lumbar area
M5486	other back pain: lumbar area
M5487	other back pain: lumbar-sacral area
M5488	other back pain: sacral area
M5489	other back pain: not detailed localisation
M5490	back pain- nondetailed specification: several localisations of the spine
M5491	back pain- no detailed specification: atlanto-occipital joint
M5492	back pain- no detailed specification: cervical area
M5493	back pain- no detailed specification: cervical-thoracic area
M5494	back pain- no detailed specification: thoracic area
M5495	back pain- no detailed specification: thoracic-lumbar area
M5496	back pain- no detailed specification: lumbar area
M5497	back pain- no detailed specification: lumbar-sacral area
M5498	ankle and foot (tarsal, metatarsal, toes, ankle, subtalar joint, other ankle joints)
M5499	back pain- not detailed specification: area not detailed localisation
M7960	pain in extremities: several localisations
M7961	pain in extremities: shoulder region (clavícula, scapula, acromioclavicular-/shoulder-/sternoclavicular joint)
M7962	pain in extremities: upper arm (humerus, elbow joint)
M7963	pain in extremities: forearm (radius, ulna, wrist)
M7964	pain in extremities: hand (finger, carpus, metacarpus)
M7965	pain in extremities: pelvic region and thigh (pelvis, femur, buttocks, hip, hip joint, sacroiliac joint)
M7966	pain in extremities: lower leg (fibula, tibia, knee joint)
M7967	pain in extremities: ankle and foot (tarsal, metatarsal, toes, ankle, subtalar joint, other ankle joints)
M7969	pain in extremities: no detailed localisation
M961	post dissection syndrome
N3981	flank pain
N940	intermenstrual pain
O294	headache after spinal cord anesthesia during pregnancy
O745	headache after spinal cord anesthesia during pregnancy
O894	headache after spinal cord anesthesia during childbirth
R070	sore throat

R071	chest pain while breathing
R072	precordial pain
R073	other kind of chest pain
R074	chest pain: no detailed specification
R101	pain in the area of upper abdomen
R102	pain in the area of pelvis and perineum
R103	pain in other areas of lower abdomen
R104	other pains without detailed specification
R309	pains passing water without detailed specification
R51	headache
R520	acute pain
R521	chronic unswayable pain
R522	other chronic pain
R529	pain without detailed specification
ICD-10 pain codes “typically neuropathic” (Diagnoses with an improved evidence via controlled randomised studies)	
B02	herpes zoster
G500	trigeminal neuralgia
G530	post zoster neuralgia
G546	phantom pain
G9585	deafferentation pain due to spinal cord impairment
M797	fibromyalgia
T926	stump pain after traumatically arm amputation
T936	stump pain after traumatically leg amputation
ICD-10 pain code “possibly neuropathic” (diseases with a potentially neuropathic genesis based upon aetiology/anatomical deliberations, independent from the therapeutic benefit of P/G according to the guideline “diagnostic for neuropathic pain” from the German Society of Neurology [1])	
G130	paraneoplastic neuromyopathy and neuropathy
G521	diseases of N. glossopharyngeus and glossopharyngeus neuralgia
G56	mono neuropathy of the upper extremity
G57	mono neuropathy of the lower extremity
G58	other mono neuropathies
G59	mono neuropathy parallel to other illness
G60	hereditary and idiopathic neuropathy
G61	polyneuritis
G62	other polyneuropathies
G63	polyneuropathy parallel to other illness
G990	autonomous neuropathy through endokrinal and metabolic diseases
M501	cervical intervertebral disc degeneration with radiculopathy
M511	lumbal intervertebral disc degeneration with radiculopathy
M541	radiculopathy
M542	cervical neuralgia
M543	ischialgia
M544	lumboischialgia

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5-8
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	Cross sectional study
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-8
Bias	9	Describe any efforts to address potential sources of bias	5-8
Study size	10	Explain how the study size was arrived at	Secondary data analysis
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Cross sectional study
		(b) Describe any methods used to examine subgroups and interactions	5-8
		(c) Explain how missing data were addressed	5-8
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	5-8

		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	
			Cross sectional study
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9-11 Secondary data analysis Secondary data analysis
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	9-11 9-11 Cross sectional study
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	Cross sectional study Cross sectional study 9-11
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Cross sectional study 9-11 9-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Cross sectional study
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13-14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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BMJ Open

Prescribing practice of pregabalin / gabapentin in pain therapy – an evaluation of German claim data

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**Prescribing practice of pregabalin / gabapentin in pain therapy
– an evaluation of German claim data**

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40 Abstract

41 **Objectives:** To describe the prevalence and incidence of pregabalin and gabapentin (P/G)
42 prescriptions, typical therapeutic uses of P/G with careful attention to pain-related diagnoses, and
43 discontinuation rates of P/G.

44 **Design:** A secondary data analysis.

45 **Setting:** Primary and secondary care in Germany.

46 **Participants:** Anonymous health insurance data of 4 million insured persons in the space of time from
47 2009 to 2015.

48 **Intervention:** None.

49 **Primary and secondary outcome measures:** We analysed the prescribing practice of P/G in general
50 and investigate the use of P/G in pain therapy. We focused on the question due to which pain-related
51 diagnoses patients get a new P/G prescription and illustrated the discontinuation rate of P/G.

52 **Results:** In 2015, 1.6% of insured persons were given a P/G prescription. Among the pain patients
53 with new P/G prescriptions, only 25.7% had a typical neuropathic pain disorder. For the remaining
54 new P/G recipients (74.3%), there was either no diagnosis of neuropathic pain or a diagnosis in which
55 a neuropathic component was conceivable pathophysiologically, but with no evidence for the use of
56 P/G. The rate of discontinuation for P/G was high (85%). Among the patients who had discontinued
57 medication, 61.1% did not receive one follow-up prescription within two years.

58 **Conclusion:** The results show that P/G is widely used in cases of chronic pain irrespective of
59 neuropathic pain diagnoses. The high rate of discontinuation indicates that the anticipated therapeutic
60 effects are lacking and/or adverse effects occur.

61 **Trial registration:** None.

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3 **62 Strengths and limitations of this study**
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- 5 **63** • A secondary data analysis can lead to systematic restrictions.
6 **64** • Diagnosis may have been insufficiently coded (documentation errors).
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8 **65** • The diagnosis coding of unspecific low back pain were often routinely coded as
9 "lumboischialgia" or unspecific neck pain as "cervical neuralgia", which can cause a
10 **66** systematic misclassification tend towards overestimation of neuropathic diagnosis.
11 **67**
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13 **68** • We cannot conclude about the reasons of the detected prescribing practice.
14 **69** • According to the secondary nature of the data, we have no information about the
15 discontinuation reasons of P/G.
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71 1. Introduction

72 Pregabalin and gabapentin, hereinafter referred to as pregabalin/gabapentin or P/G, belong to the
73 group of "newer antiepileptic drugs", which were developed for the treatment of epilepsy. The
74 European Medicines Agency approved pregabalin/gabapentin later also for the treatment of
75 neuropathic pain (pregabalin (2004): "peripheral and central neuropathic pain"; gabapentin (2001):
76 "peripheral neuropathic pain like painful diabetic neuropathy and post herpetic neuralgia" [1, 2]),
77 which is now a common indication for these active ingredients [3].
78 Randomised controlled studies showed a slight improvement of specific forms of neuropathic pain
79 disorder in patients treated with pregabalin/gabapentin compared to placebo [4–6]. The evidence for
80 the rather small therapeutic effects of P/G, which are approved for the treatment of a rather minor
81 condition spectrum, contradicts the prescription figures, which have been increasing steadily for years.
82 According to the medication report, a total of 128 million daily doses of pregabalin/gabapentin were
83 prescribed in 2015 [3]. The Lyrica product by Pfizer (pregabalin) was ranked 26th in 2015 on the list
84 of the highest-revenue medicines under patent-protection with net GKV (statutory health insurance)
85 costs of 170.3 million Euros [3]. US Prescription data describe the same trends. The gabapentin
86 prescription rate has been raised from 39 million in 2012 to 64 million in 2016 in the United States [7,
87 8].

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89 Increased P/G prescribing prompted us to further investigate prescribing practices. In this study, we
90 answer the following questions:

- 91 1.) How high is the **annual prevalence** for the prescription of pregabalin/gabapentin among all
92 insured persons from 2009 to 2015?
- 93 2.) How high is the **annual incidence** for new prescriptions of pregabalin/gabapentin among all
94 insured persons from 2009 to 2015?
- 95 3.) What are the **indications for prescribing** (epilepsy/generalised anxiety disorder/pain) for patients
96 with new pregabalin/gabapentin prescriptions from 2009 to 2015?
- 97 4.) Which **pain-related diagnoses** (neuropathic pain/non-neuropathic pain/mixed pain/no pain) are
98 applicable to patients without epilepsy diagnosis with new pregabalin/gabapentin prescriptions in
99 2015?
- 100 5.) What is the **proportion** of patients for whom pregabalin/gabapentin was discontinued within two
101 years after a new prescription for the treatment of pain?
102 - How many follow-up prescriptions were given to patients for whom pregabalin/gabapentin
103 was discontinued?

104 2. Methods

105 2.1. Study design and database

106 The research questions were analysed in a cross-sectional design. The research database of the InGef –
107 Institute for Applied Health Research was used as the data basis for this project. The InGef research
108 database (formerly HRI Research Database) contains data on the utilisation and resource consumption
109 of approx. 6.7 million anonymous insured persons from around 65 health insurance funds and
110 company health insurance funds [9]. As long as the insured persons are members of these health
111 insurances, their data are all-encompassing available in this database and were no competing to other
112 databases. When insurant change to another insurance which is not linked with this database, their data
113 are not available in this database. The present analysis was based on a sample of almost 4 million
114 random samples from the research database, which closely represents the age and gender structure of
115 Germany for the year 2013 (according to Destatis – Federal Statistical Office – 31.12.2013). The
116 random sampling enables a longitudinal analysis of insured persons over the years 2009-2015. Beside
117 sociodemographic data, it contains information on medicines prescribed by doctors and dispensed by
118 pharmacies in the form of central pharma numbers (PZN) and ATC codes, ICD diagnoses from
119 outpatient and inpatient areas as well as invoiced medical services.
120 The diagnoses and prescriptions can be linked to the anonymous insured person's name at the end of
121 each quarter. In every analysis, all dosage forms and formulations of P/G were included.

123 2.2. Random sample analysis

124 The inclusion criteria, which vary according to the question, are presented below (for insured persons
125 who meet the following criteria):

127 **Sample 1** (Question 1 – ANNUAL PREVALENCE):

128 Persons who were insured for at least one day in the first quarter of the respective reporting year.

130 **Sample 2** (Question 2 – ANNUAL INCIDENCE):

131 Persons who were insured for at least one day in the first quarter of the respective reporting year and
132 365 days in the previous year.

134 **Sample 3** (Question 3 – INDICATIONS FOR PRESCRIBING FOR NEW PRESCRIPTION):

135 Persons who were insured for at least one day in the first quarter of the respective reporting year and
136 365 days in the previous year with at least one pregabalin/gabapentin prescription (ATC code:
137 N03AX12 or N03AX16) in the reporting year, but not in the four previous quarters (independent from
138 diagnosis).

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Sample 4 (Question 4 – PAIN DIAGNOSES IN THE NEW PRESCRIPTION):

Persons who were insured for at least one day in the first quarter of 2015 and fulfil the following criteria: no coded epilepsy diagnosis (G40.- | G41.-) in the years 2014-2015; no prescription of antiepileptic medication (all N03 codes) in 2014; at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16) in 2015

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Sample 5 (Question 5 – DISCONTINUATION):

Persons who were insured for at least one day in the first quarter of 2013 and fulfil the following criteria: no coded epilepsy diagnosis (G40.- | G41.-) in the years 2011-2013; no prescription of antiepileptic medication (all N03 codes) in the years 2011-2012; at least one pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16), and in the same quarter of the prescription, at least one pain diagnosis in 2013

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2.3 Data evaluation

The annual prevalence was calculated individually for each reporting year from 2009 to 2015. All insured persons who received at least one P/G prescription (ATC code: N03AX12 or N03AX16) within one year were divided by the total number of all insured persons from sample 1 of the respective reporting year.

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The annual incidence was calculated individually for each year from 2010 to 2015 (except for the first reporting year: 2009, as no new prescriptions could be identified due to missing data for the previous year). To this end, all insured persons who received a pregabalin/gabapentin prescription (ATC code: N03AX12 or N03AX16) within one year, but not in the previous year, were compared to the total number of all patients from sample 2 of the respective reporting year.

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The areas of indications for P/G prescribing were analysed individually for each possible combination of the diagnoses "Epilepsy (G40.- | G41.-)", "Generalised anxiety disorder (F41.1)" and "Pain (all ICD-codes of pain syndromes)". The used pain related ICDs are illustrated in the supplementary material. In addition, insured persons in sample 3, to whom one of the above-mentioned diagnosis groups was assigned in parallel to the P/G prescription within a quarter, were divided by all insured persons in sample 3. These calculations were made individually for each reporting year from 2010 to 2015.

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To answer the question of which pain-related diagnoses P/G was newly prescribed, the percentage distribution of all coded ICD-10 pain diagnoses of the insured persons from sample 4 was presented first. Furthermore, the diagnoses were classified into the following three categories: Diagnoses with an improved evidence for P/G via controlled randomised studies (assessed by the authors) were classified

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3 176 as "**typical neuropathic pain** disorders for which there is a demonstrable **benefit of a P/G** therapy"
4 [3–6]. Diseases with a potentially neuropathic genesis based upon aetiology/anatomical deliberations,
5 177 independent from the therapeutic benefit of P/G [10] were classified as "pain, **possibly of neuropathic**
6 178 or partial-neuropathic cause for which there is **no demonstrable benefit of P/G**". All other pain
7 179 diagnose, were labelled as "**non-neuropathic** pain".
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12 182 The calculation of the number of follow-up prescriptions/rate of discontinuation according to new P/G
13 183 prescriptions was based on sample 5 and relates to the year 2013 plus two years of follow-up
14 184 observation period (up to max. 2015). If in the two-year follow-up period no P/G prescription occurred
15 185 for at least two consecutive quarters, this was defined as a discontinuation of therapy. The percentage
16 186 of insured persons who discontinued therapy and the number of individual prescriptions up to
17 187 termination were presented.
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19 189 **2.4 Patient and Public Involvement**

20 190 This is a retrospective, secondary data analysis, so patients and the public were not involved directly.
21 191 Beside this publication, we present the data of this analysis on conferences.
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192 3. Results

193 3.1. Prevalence and incidence for P/G prescriptions

194 From 2009-2015, 1.3% (52,774/3,948,482) of insured persons were prescribed at least one P/G
 195 prescription. The prevalence of prescriptions increased from 1.1% in 2009 to 1.6% per annum in 2015
 196 (Table 1a).
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Table 1a: Annual prevalence for pregabalin/gabapentin prescriptions 2009-2015			
Year	Number of insured persons with P/G prescriptions	Number of total insured persons	Prevalence per 100,000 insured persons
2009	41,083	3,822,333	1,074.8
2010	46,225	3,890,247	1,188.2
2011	50,230	4,027,591	1,247.1
2012	53,389	4,019,944	1,328.1
2013	56,358	4,010,383	1,405.3
2014	60,306	3,998,004	1,508.4
2015	61,828	3,870,869	1,597.3
Mean value 2009-2015	52,774	3,948,482	1,335.6

Table 1b: Prevalence for pregabalin/gabapentin prescriptions grouped by age and stratified by gender in 2015

Age group	Total prevalence per 100,000 insured persons	Prevalence per 100,000 insured women	Prevalence per 100,000 insured men
0-17	13.4	17.5	9.6
18-35	249.2	289.4	210.0
36-55	1,042.5	1,213.2	874.9
56-75	2,899.6	3,146.0	2,634.9
76+	5,302.1	5,709.5	4,658.1
Total	1,597.3	1,869.7	1,312.8
Total 18+	1,894.0	2,197.1	1,571.7

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 199 The prescription rate was highest in the 76+ age group (5,302 persons per 100,000 insured persons in
 200 2015) (Table 1b). The prescription for minors, on the other hand, at 13.4 per 100,000 insured persons,
 201 was low. Compared to men, women were prescribed P/G more frequently (women: a total of 1,869.7
 202 per 100,000 insured persons; men: a total of 1,312.8 per 100,000 insured persons). Like prescription
 203 prevalence, the rate of new P/G prescription increased annually (Table 2).

Table 2: **Annual incidence** for pregabalin/gabapentin – new prescriptions 2010-2015

Year	Number of insured persons with new P/G prescriptions	Number of total insured persons	Incidence per 100,000 insured persons
2010	22,776	3,701,696	615.3
2011	23,121	3,717,582	621.9
2012	24,750	3,977,347	622.3
2013	25,784	3,966,813	650.0
2014	27,613	3,952,306	698.7
2015	26,526	3,757,502	705.9
Mean value 2010-2015	25,095	3,845,541	652.4

3.2. Area of application

Considering the three applications approved for P/G, it was found that the majority (77.9%) of P/G recipients had only a pain diagnosis and there was no evidence of epilepsy or anxiety disorder (Table 3).

Table 3: **Diagnoses** in patients with pregabalin/gabapentin prescriptions in 2015 (n=61,828)

ICD diagnoses	Number of insured persons with P/G prescriptions	As a percentage
Pain * (exclusive)	48,190	77.9
Epilepsy ** (exclusive)	793	1.3
Anxiety disorder *** (exclusive)	707	1.1
Pain + anxiety disorder	2,404	3.9
Pain + epilepsy	2,222	3.6
Pain + epilepsy + anxiety disorder	162	0.3
Epilepsy + anxiety disorder	49	0.1
No pain, epilepsy or anxiety disorder	7,198	11.6
* all ICD-10 pain diagnoses listed in the supplementary information		
** ICD codes: G40.- G41.-		
*** ICD codes: F41.1		

There was no evidence for the approved application diagnoses for 11.6% of the P/G recipients. P/G recipients exclusively with a diagnosis of epilepsy or anxiety (epilepsy: 1.3%; anxiety 1.1%) were the minority. The percentage of new P/G recipients (excluding pain diagnoses) increased continuously

214 over the years. The proportion of existing epilepsy and anxiety diagnoses remained relatively constant
215 in the new P/G prescriptions group.

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217 3.3. Application in pain patients

218 After excluding epilepsy patients, 25,251 insured persons remained under new P/G prescription,
219 whose pain diagnoses were analysed. A typical neuropathic pain disorder was present in one quarter of
220 all new P/G recipients (25.7%), Table 4.

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Table 4: Pain-related diagnoses in patients with new pregabalin/gabapentin prescriptions in 2015 (n=25,251)			
Pain-related diagnoses		Number of insured persons	As a percentage
1	Non-neuropathic pain * (exclusive)	2,951	11.7
2	Typical neuropathic pain disorder ** (exclusive) (demonstrable benefit of a P/G therapy)	1,218	4.8
3	Pain with possible neuropathic or partial-neuropathic cause *** (exclusive) (no demonstrable benefit of P/G)	3,025	12.0
1 and 2		1,295	5.1
1 and 3		10,756	42.6
2 and 3		1,010	4.0
1 and 2 and 3		2,990	11.8
neither 1, 2 nor 3		2,006	7.9

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223 For the majority (70.4%) of new recipients, a diagnosis was made in which a neuropathic component
224 was conceivable pathophysiologically, but with no evidence for the use of P/G. The three most
225 frequent representatives in this category were the diagnoses "M544_Lumboischialgia"
226 (5,836/25,251), "M5416_Radiculopathy: Lumbar region" (4,978/25,251) and "M542_Cervical
227 neuralgia" (4,543/25,251). In 19.6% of the cases, there was exclusively only a "non-neuropathic pain
228 diagnosis" or "no pain diagnosis".

229 The percentage distribution of the pain-related diagnoses showed slightly variation over the time. The
230 portion of typical neuropathic pain disorders was 17.8% in 2011 and 18.6% in 2013; the portion of
231 pain disorder with a potentially neuropathic component was 72.4 in 2011 and 73.8% in 2013; the
232 portion of cases with "non-neuropathic pain diagnosis" or "no pain diagnosis" war 18.8% in 2011 and
233 20.6% in 2013.

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235 **3.4. Discontinuation**

236 Within the follow-up period, 85% (16,573/19,501) of insured persons who received a new P/G
237 prescription due to pain (excluding patients with epilepsy diagnosis) were again discontinued within
238 two years. For the majority of the persons, who have discontinued, the discontinuation occurred within
239 a short period. Thus, in 61.1% of the cases, there was no follow-up prescription after the initial
240 prescription (number of follow-up-prescriptions / proportion in percent: 1/13.2%; 2/7.5%; 3/5.4%;
241 $\geq 4/12.8\%$). The proportion of P/G insured persons with regular follow-up prescriptions over the
242 follow-up period was 15% (2,928/19,501).

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4. Discussion

The prescription figures for pregabalin and gabapentin increased annually from 2009 to 2015. The majority of patients (78%), who are receiving P/G, have a pain diagnosis. In patients who received new P/G prescriptions, only about one quarter (25.7%) had a typical neuropathic pain disorder with a demonstrable benefit of a P/G therapy. For the remaining new P/G recipients (74.3%), there was either no diagnosis of neuropathic pain or a diagnosis in which a neuropathic component was conceivable pathophysiologically, but with no evidence for the use of P/G. The rate of discontinuation for P/G was high; based on new prescriptions, 51.9% of cases did not receive a follow-up prescription within two years.

The increasing number of P/G prescriptions found in this analysis coincides with data from the IMS health database from the United States [7, 8]. Goodman et al. state in an issue of the New England Journal of Medicine in August 2017, that growth of P/G prescriptions was likely in “chronic non-cancer pain” as an alternative to opiates [8]. Although the incidence of purely neuropathic pain disorders has been slightly increased in the last years, the extent of the increasing number of P/G prescriptions does not disproportionate. The steadily increasing number of prescriptions indicates that P/G is increasingly being used in patients with “mixed chronic pain” (mixed pain). “Mixed pain” refers to chronic pain syndromes in which a mixture of nociceptive and neuropathic pain components is assumed [11, 12]. Instruments specially developed for this purpose, such as the painDETECT questionnaire, are designed to identify the neuropathic pain component [13] and are promoted accordingly. However, the pre-approval P/G studies only included patients with pure neuropathic pain as a result of damage to somatosensory nerve structures, e.g. with post-zoster neuralgia or diabetic polyneuropathy. High-quality qualitative studies on the efficacy of P/G in patients with mixed chronic pain are not yet available [14]. In the current edition of the guideline “Non-specific low back pain”, the NVL guideline group also opposes a screening using painDETECT [15] due to a lack of evidence. The increasing prescribing rate among elderly might depend on the fact that chronic pain diagnosis generally increases by age [16].

In consideration of the pain diagnoses, which are coded in parallel to new P/G prescriptions, the question arises as to which diagnoses should be classified as neuropathic or non-neuropathic. In the S1 guideline “Diagnostics of neuropathic pain” [10] of the German Society of Neurology, for example, in addition to the pure neuropathic pain syndromes with damage to somatosensory nerve structures, pain diagnoses in which a neuropathic component is pathophysiologically conceivable, such as “lumboischialgia” or “radiculopathy”, are classified as neuropathic. The pain of these conditions is typically caused by nerve irritation, but this does not necessarily constitute damage. In these cases, there is often no evidence of benefit for the application of P/G. In this regard, an RCT published in March 2017 by Mathieson et al. showed the non-benefit of Pregabalin [17]. Within the

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3 280 scope of this project, we decided to differentiate between "typical neuropathic pain disorder" with a
4 281 demonstrable benefit of P/G therapy and "pain, possibly with neuropathic or partially-neuropathic
5 282 cause" with no evidence for the application of P/G. Subsequently, a typical neuropathic pain disorder
6 283 is presented exclusively in one fifth of the new P/G prescriptions. This phenomenon is increasingly
7 284 being described and critically discussed internationally [8, 18]. Abroad, there is also an increasing
8 285 evidence of P/G as drugs of abuse [19, 20].

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14 287 Due to the nature of a routine data analysis, we are finally not able to perceive the real reasons for the
15 288 high discontinuation rate on the base of this routine data. P/G might have been discontinued because of
16 289 adverse effects, the resolution of pain by the reason that the hoped for pain-relieving effect has not
17 290 been achieved. We speculate, that the high discontinuation rate reflects an ineffectiveness of P/G in
18 291 chronic pain therapy.

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24 293 The discrepancy between the high number of prescriptions and the discontinuation rate, as a
25 294 potentially indirect parameter of a clinically unconvincing effect, raises the question of why a drug
26 295 that is seen as ineffective might be so readily prescribed? Due to the complex nature of the doctor-
27 296 patient-interaction while the treatment of chronic pain disorders, doctors might resort to second line
28 297 medication to help their patients. Furthermore, the marketing by the pharmaceutical industry [8],
29 298 among others, which was specifically targeted at the treatment of mixed-pain patients with neuropathic
30 299 symptoms, may play an important role.

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36 301 Altogether, the results of this analysis provide an indication of overprescribing of P/G. In
37 302 consequence, several patients probably take unnecessary drugs going along with the typical
38 303 polypharmacy risks (e.g. side effects, drug-drug interactions). Furthermore, overprescribing carries a
39 304 high economic burden for the health care system. For example, the costs for pregabalin has been
40 305 doubled from 2012 to \$4.4 billion in 2016 in the United States [7, 8]. German data describe the same
41 306 trends [3]. There are possible savings for health insurance funds.

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47 308 The secondary data analysis, which is based on accounting data on the utilisation of insured persons
48 309 from health insurance funds, can lead to systematic restrictions [21]. The variable "P/G consumption"
49 310 can be considered as a valid indicator because P/G is only available on prescription. However, the
50 311 operationalisation of the pain-related diagnosis variables is more challenging due to the fact, that the
51 312 diagnosis coding maybe insufficiently coded in individual cases. One possibility are random errors
52 313 during the diagnosis coding, which result in a potential bias in both directions (more or less than in
53 314 reality). Another possibility may be, that doctors prefer to code clear neuropathic diagnoses to justify
54 315 the prescription even in cases where the neuropathic nature is unclear. This might result in a bias,
55 316 where the proportion of evidence-based indications is even lower in reality. In the diagnosis coding of

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3 317 unspecific low back pain as well, systematic misclassifications that tend towards overestimation are
4 318 likely, since they are often routinely coded as "lumboischialgia" / "Radiculopathy: Lumbar region" or
5 319 unspecific neck pain as "cervical neuralgia".

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8 320 According to international literature, P/G has also sometimes used in off-label indications like hot
9 321 flush, restless leg, multiple sclerosis [22]. Our methodologically approach, does not account these
10 322 potentially off label indications, which may lead to a bias. Patients would be mistakenly assumed to be
11 323 using P/G for a non-neuropathic pain condition, when in fact they were using it for such an off-label
12 324 indication.

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16 326 Conclusion:

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19 327 Our analysis indicates that the increasing use of pregabalin and gabapentin is not in typical
20 328 neuropathic pain conditions. Furthermore, high rates of discontinuation suggest that anticipated
21 329 therapeutic effects are lacking and/or adverse effects occur. Clinicians and patients should exercise
22 330 caution with regard to the use.

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3 331 **5. Study protocol**

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6 332 The study protocol is available on request. Please contact: annika.viniol@staff.uni-marburg.de.
7

8 333 **6. Funding**

9
10 334 This research received no specific grant from any funding agency in the public, commercial or not-for-
11
12 335 profit sectors.
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15 336 **7. Competing interests**

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17 337 The authors declare that they have no competing interests.
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20 338 **9. Authors' contributions**

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22 339 AV planned the study, discussed the results and wrote the manuscript. TP and LH analyzed data and
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24 340 discussed the manuscript. KMK gave support to study design and discussed the manuscript. JW, JH,
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26 341 NDB and AB discussed the results and the manuscript.
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28 342 **10. Reporting statement**

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30 343 Data analysis and reporting style is in accordance with the “German Reporting Standard for Secondary
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32 344 Data Analyses” (STROSA).
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35 345 **11. Patient consent**

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37 346 Due to the nature of secondary data analysis, no patient consent is required.
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41 347 **12. Data sharing statement**

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43 348 Data used in the analyses are entrusted in the Institute for Applied Health Research Berlin. Please
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45 349 contact: jochen.walker@hrisk.de
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The classification criteria of the pain-related diagnosis

ICD-10 pain code “not neuropathic”

F413	fear/tension- type pain syndrome
F4534	psychogenic painful micturition
F4539	psychogenic pain of the abdomen
F4540	continuing somatoform disorder
F4541	chronic pain with somatic and psychological factors
G440	cluster headache
G441	vasomotor headache
G442	tension headache
G443	chronic posttraumatic headache
G444	headache caused by drugs
G448	other headache without detailed specification
G501	atypical facial pain
H571	eye pain
I702	arteriosclerosis of the extremities: physical stress induced leg pain
L905	cicatix pain
M2550	joint pain: multiple sites
M2551	joint pain: shoulder region (clavicula, scapula, acromioclavicular-/shoulder-/sternoclavicular joints)
M2552	joint pain: upper arm (humerus, elbow joint)
M2553	joint pain: forearm (radius, ulna, wrist)
M2554	joint pain: hand (finger, carpus, metacarpus)
M2555	joint pain: pelvic region and thigh (pelvis, femur, buttocks, hip, hip joint, sacroiliac joint)
M2556	joint pain: lower leg (fibula, tibia, knee joint)
M2557	joint pain: ankle and foot (tarsal, metatarsal, toes, ankle, subtalar joint, other ankle joints)
M2558	joint pain: multiple sites (neck, head, ribs, torso, spine)
M2559	joint pain: multiple localisation
M545	back pain
M546	pain in area of thoracic spine
M5480	other back pain: different areas of the spine
M5481	other back pain: atlanto-occipital joint
M5482	other back pain: cervical area
M5483	other back pain: cervical-thoracic area
M5484	other back pain: thoracic area
M5485	other back pain: thoracic-lumbar area
M5486	other back pain: lumbar area
M5487	other back pain: lumbar-sacral area
M5488	other back pain: sacral area
M5489	other back pain: not detailed localisation
M5490	back pain- nondetailed specification: several localisations of the spine
M5491	back pain- no detailed specification: atlanto-occipital joint
M5492	back pain- no detailed specification: cervical area
M5493	back pain- no detailed specification: cervical-thoracic area
M5494	back pain- no detailed specification: thoracic area
M5495	back pain- no detailed specification: thoracic-lumbar area
M5496	back pain- no detailed specification: lumbar area
M5497	back pain- no detailed specification: lumbar-sacral area
M5498	ankle and foot (tarsal, metatarsal, toes, ankle, subtalar joint, other ankle joints)
M5499	back pain- not detailed specification: area not detailed localisation
M7960	pain in extremities: several localisations
M7961	pain in extremities: shoulder region (clavicula, scapula, acromioclavicular-/shoulder-/sternoclavicular joint)
M7962	pain in extremities: upper arm (humerus, elbow joint)
M7963	pain in extremities: forearm (radius, ulna, wrist)
M7964	pain in extremities: hand (finger, carpus, metacarpus)
M7965	pain in extremities: pelvic region and thigh (pelvis, femur, buttocks, hip, hip joint, sacroiliac joint)
M7966	pain in extremities: lower leg (fibula, tibia, knee joint)
M7967	pain in extremities: ankle and foot (tarsal, metatarsal, toes, ankle, subtalar joint, other ankle joints)
M7969	pain in extremities: no detailed localisation
M961	post dissection syndrome
N3981	flank pain
N940	intermenstrual pain
O294	headache after spinal cord anesthesia during pregnancy
O745	headache after spinal cord anesthesia during pregnancy
O894	headache after spinal cord anesthesia during childbirth
R070	sore throat

R071	chest pain while breathing
R072	precordial pain
R073	other kind of chest pain
R074	chest pain: no detailed specification
R101	pain in the area of upper abdomen
R102	pain in the area of pelvis and perineum
R103	pain in other areas of lower abdomen
R104	other pains without detailed specification
R309	pains passing water without detailed specification
R51	headache
R520	acute pain
R521	chronic unswayable pain
R522	other chronic pain
R529	pain without detailed specification
ICD-10 pain codes “typically neuropathic” (Diagnoses with an improved evidence via controlled randomised studies)	
B02	herpes zoster
G500	trigeminal neuralgia
G530	post zoster neuralgia
G546	phantom pain
G9585	deafferentation pain due to spinal cord impairment
M797	fibromyalgia
T926	stump pain after traumatically arm amputation
T936	stump pain after traumatically leg amputation
ICD-10 pain code “possibly neuropathic” (diseases with a potentially neuropathic genesis based upon aetiology/anatomical deliberations, independent from the therapeutic benefit of P/G according to the guideline “diagnostic for neuropathic pain” from the German Society of Neurology [1])	
G130	paraneoplastic neuromyopathy and neuropathy
G521	diseases of N. glossopharyngeus and glossopharyngeus neuralgia
G56	mono neuropathy of the upper extremity
G57	mono neuropathy of the lower extremity
G58	other mono neuropathies
G59	mono neuropathy parallel to other illness
G60	hereditary and idiopathic neuropathy
G61	polyneuritis
G62	other polyneuropathies
G63	polyneuropathy parallel to other illness
G990	autonomous neuropathy through endokrinal and metabolic diseases
M501	cervical intervertebral disc degeneration with radiculopathy
M511	lumbal intervertebral disc degeneration with radiculopathy
M541	radiculopathy
M542	cervical neuralgia
M543	ischialgia
M544	lumboischialgia

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5-8
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	Cross sectional study
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-8
Bias	9	Describe any efforts to address potential sources of bias	5-8
Study size	10	Explain how the study size was arrived at	Secondary data analysis
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Cross sectional study
		(b) Describe any methods used to examine subgroups and interactions	5-8
		(c) Explain how missing data were addressed	5-8
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	5-8

		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	
			Cross sectional study
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9-11 Secondary data analysis Secondary data analysis
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	9-11 9-11 Cross sectional study
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	Cross sectional study Cross sectional study 9-11
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Cross sectional study 9-11 9-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Cross sectional study
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13-14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prescribing practice of pregabalin / gabapentin in pain therapy – an evaluation of German claim data

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5 2 **Prescribing practice of pregabalin / gabapentin in pain therapy**
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40 Abstract

41 **Objectives:** To analyse the prevalence and incidence of pregabalin and gabapentin (P/G)
42 prescriptions, typical therapeutic uses of P/G with special attention to pain-related diagnoses and
43 discontinuation rates.

44 **Design:** Secondary data analysis.

45 **Setting:** Primary and secondary care in Germany.

46 **Participants:** 4 million patients in the years 2009-2015 (Anonymous health insurance data).

47 **Intervention:** None.

48 **Primary and secondary outcome measures:** P/G prescribing rates, P/G prescribing rates associated
49 with pain therapy, analysis of pain-related diagnoses leading to new P/G prescriptions and the
50 discontinuation rate of P/G.

51 **Results:** In 2015, 1.6% of insured persons received P/G prescriptions. Among the pain patients firstly
52 treated with P/G, as few as 25.7% were diagnosed with a typical neuropathic pain disorder. The
53 remaining 74.3% had either not received a diagnosis of neuropathic pain or showed a neuropathic
54 component that was pathophysiologically conceivable but did not support the prescription of P/G.
55 High discontinuation rates were observed (85%). Among the patients who had discontinued the drug,
56 61.1% did not receive follow-up prescriptions within two years.

57 **Conclusion:** The results show that P/G is widely prescribed in cases of chronic pain irrespective of
58 neuropathic pain diagnoses. The high discontinuation rate indicates a lack of therapeutic benefits
59 and/or the occurrence of adverse effects.

60 **Trial registration:** None.

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3 61 **Strengths and limitations of this study**
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- 5 62 • Secondary data analysis can lead to systematic restrictions.
6 63 • Diagnosis may have been coded incorrectly, resulting in either under- or overestimation of
7 64 neuropathic diagnoses.
8 65 • According to the secondary nature of our data, we cannot conclude about the reasons of the
9 66 detected prescribing practice.
10 67 • We have no information about the discontinuation reasons of P/G.
11 68 • Our methodological approach does not include off-label indications of P/G.
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1. Introduction

Pregabalin and gabapentin, hereinafter referred to as pregabalin/gabapentin or P/G, belong to the group of "newer antiepileptic drugs". As chemical analogues of the inhibitory neurotransmitter GABA (gamma-aminobutyric acid) they are classified as "gabapentinoids". Originally developed for the treatment of epilepsy, the European Medicines Agency (EMA) approved P/G also for the treatment of neuropathic pain (pregabalin (2004): "peripheral and central neuropathic pain"; gabapentin (2001): "peripheral neuropathic pain like painful diabetic neuropathy and post herpetic neuralgia" [1, 2]), which is now a common indication for their prescription [3].

Randomised controlled studies reported a slight improvement in specific forms of neuropathic pain disorder for patients treated with pregabalin/gabapentin compared to placebo [4–6]. However, the obviously rather weak therapeutic effects of P/G and their comparatively small application area are contradicted by the prescription figures, which have been increasing steadily over the recent years. According to the German 'medication report' from Schwabe et al. (based on statutory health insurance data), a total of 128 million daily doses of pregabalin/gabapentin were prescribed in 2015 [3]. In 2015, Pfizer's product Lyrica (pregabalin) was ranked 26th on the list of the highest-revenue medicines under patent-protection and produced net GKV (statutory health insurance) costs of 170.3 million Euro [3]. US Prescription data describe the same trends: from 2012 to 2016, the prescription rate of gabapentin increased from 39 to 64 million annual prescriptions. [7, 8].

In view of this general trend, we intended to further investigate the prescribing practices. This study aims to address the following points in question:

- 1.) The **annual prevalence** for the prescription of pregabalin/gabapentin among all insured persons from 2009 to 2015
- 2.) The **annual incidence** for new prescriptions of pregabalin/gabapentin among all insured persons from 2009 to 2015
- 3.) The **indications for new** pregabalin/gabapentin prescriptions (epilepsy/generalised anxiety disorder/pain) from 2009 to 2015
- 4.) **The Pain related diagnoses** (neuropathic pain/non-neuropathic pain/mixed pain/no pain) that lead to new pregabalin/gabapentin prescriptions to patients without epilepsy in 2015
- 5.) **The proportion** of patients who **discontinued** pregabalin/gabapentin **treatment within two years** after its new prescription for pain management and the **proportion of follow-up prescriptions** after discontinuation.

102 2. Methods

103 2.1. Study design and database

104 For this project, the Institute for Applied Health Research (InGef) database was analysed in a cross-
105 sectional design. This research database (formerly HRI Research Database) contains anonymous data
106 on the utilisation and resource consumption of approx. 6.7 million insured persons from about 65
107 health insurance funds and company health insurance funds [9]. As long as the insured persons are
108 members of these health insurances, their data are all-encompassing available without overlap with
109 other databases, which also means that if a person changes to an insurance that is not included, his or
110 her data become unavailable. The present analysis is based on a random sample of almost 4 million
111 data sets which closely represents the age and gender structure in Germany for the year 2013
112 (according to Destatis – Federal Statistical Office – 31.12.2013). The random sampling enables a
113 longitudinal analysis of insured persons over the years 2009-2015. Besides sociodemographic data, it
114 contains central pharma numbers (PZN) and ATC codes, ICD diagnoses from outpatient and inpatient
115 areas as well as invoiced medical services. These data give information on medications prescribed by
116 doctors and dispensed by pharmacies.
117 The diagnoses and prescriptions can be linked to the anonymous insured person's identification code at
118 the end of each quarter. Each analysis included all dosage forms and formulations of P/G.

120 2.2. Random sample analysis

121 The following inclusion criteria vary according to the point in question:

123 **Sample 1 (ANNUAL PREVALENCE):**

124 Persons who were insured for at least one day in the first quarter of the respective reporting year.

126 **Sample 2 (ANNUAL INCIDENCE):**

127 Persons who were insured for at least one day in the first quarter of the respective reporting year and
128 365 days in the previous year.

130 **Sample 3 (INDICATIONS FOR NEW PRESCRIPTION):**

131 Persons who were insured for at least one day in the first quarter of the respective reporting year and
132 365 days in the previous year with at least one pregabalin/gabapentin prescription (ATC code:
133 N03AX12 or N03AX16) in the reporting year, but not in the four previous quarters (independent from
134 diagnosis).

136 **Sample 4 (PAIN DIAGNOSES, NEW PRESCRIPTION):**

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3 137 Persons who were insured for at least one day in the first quarter of 2015 and fulfil the following
4 138 criteria: no coded epilepsy diagnosis (G40.- | G41.-) in the years 2014-2015; no prescription of
5 139 antiepileptic medication (all N03 codes) in 2014; at least one pregabalin/gabapentin prescription (ATC
6 140 code: N03AX12 or N03AX16) in 2015.
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11 142 **Sample 5 (DISCONTINUATION, NEW PRESCRIPTION):**

12 143 Persons who were insured for at least one day in the first quarter of 2013 and fulfil the following
13 144 criteria: no coded epilepsy diagnosis (G40.- | G41.-) in the years 2011-2013; no prescription of
14 145 antiepileptic medication (all N03 codes) in the years 2011-2012; at least one pregabalin/gabapentin
15 146 prescription (ATC code: N03AX12 or N03AX16), and at least one pain diagnosis in the same quarter
16 147 of the prescription in 2013.
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21 149 **2.3 Data evaluation**

22 150 The annual prevalence was calculated individually for each reporting year from 2009 to 2015. The
23 151 total of insured persons who received at least one P/G prescription (ATC code: N03AX12 or
24 152 N03AX16) within one year was divided by the number of all insured persons from sample 1 of the
25 153 respective reporting year.
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31 155 The annual incidence was calculated individually for each year from 2010 to 2015 (except for the first
32 156 reporting year 2009, as due to the lack of data for the previous year, new prescriptions could not be
33 157 identified). To this end, all insured persons who had received a pregabalin/gabapentin prescription
34 158 (ATC code: N03AX12 or N03AX16) within one year, but not in the previous year, were compared to
35 159 the total number of all patients from sample 2 of the respective reporting year.
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41 161 The areas of indications for P/G prescribing were analysed individually for each possible combination
42 162 of the diagnoses "Epilepsy (G40.- | G41.-)", "Generalised anxiety disorder (F41.1)" and "Pain (all ICD-
43 163 codes of pain syndromes)". (For the pain related ICDs included, see supplementary material). In
44 164 addition, the number of insured persons from sample 3 that were falling into one of these diagnosis
45 165 groups and had concurrently received a P/G prescription within a quarter was divided by the number
46 166 of all insured persons in sample 3. These calculations were applied to each reporting year from 2010 to
47 167 2015.
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52 169 To answer question 4, we first analysed the percentage distribution of all coded ICD-10 pain diagnoses
53 170 of the insured persons from sample 4, then classified the diagnoses into the following categories:
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- 56 171 1) Diagnoses with an improved evidence for P/G (assessed by the authors via controlled
57 172 randomised studies) were classified as "**typical neuropathic pain** disorders with
58 173 **demonstrable benefit** from P/G therapy" [3–6].
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3 174 2) Diseases from a potentially neuropathic genesis based upon aetiology/anatomical
4 175 deliberations, without therapeutic benefit of P/G [10] were classified as "pain, **possibly** of
5 176 **neuropathic** or partial-neuropathic cause for which there is **no demonstrable benefit of**
6 177 **P/G**".

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9 178 3) All other pain diagnoses were labelled as "**non-neuropathic pain**".
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12 180 To calculate the number of follow-up prescriptions and the rate of discontinuation according to new
13 181 P/G prescriptions, we analysed the sample 5 data from the year 2013 plus a follow-up observation
14 182 period of two years (until 2015). Cases in which the patient had not received a P/G prescription within
15 183 at least two consecutive quarters, including the two-year follow-up period, were defined as
16 184 discontinuation of therapy. This evaluation revealed the percentage of insured persons who
17 185 discontinued therapy and the number of individual prescriptions before termination.
18 186

19 187 **2.4 Patient and Public Involvement**

20 188 Because the present study represents a retrospective secondary data analysis, patients and the public
21 189 were not directly involved. Our work includes the presentation of our research at scientific
22 190 conferences.
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191 3. Results

192 3.1. Prevalence and incidence of P/G prescriptions

193 From 2009-2015, 1.3% (52,774/3,948,482) of insured persons received at least one P/G prescription.

194 As shown in table 1 a, the prevalence rate increased from 1.1% in 2009 to 1.6% per annum in 2015.

195

Table 1a: **Annual prevalence** rates of pregabalin/gabapentin prescriptions, 2009-2015

Year	Number of insured persons with P/G prescriptions	Total number of insured persons	Prevalence per 100,000 insured persons
2009	41,083	3,822,333	1,074.8
2010	46,225	3,890,247	1,188.2
2011	50,230	4,027,591	1,247.1
2012	53,389	4,019,944	1,328.1
2013	56,358	4,010,383	1,405.3
2014	60,306	3,998,004	1,508.4
2015	61,828	3,870,869	1,597.3
Mean value 2009-2015	52,774	3,948,482	1,335.6

Table 1b: **Prevalence** rates of pregabalin/gabapentin prescriptions in 2015, stratified by age and gender

Age group	Total prevalence per 100,000 insured persons	Prevalence per 100,000 insured women	Prevalence per 100,000 insured men
0-17	13.4	17.5	9.6
18-35	249.2	289.4	210.0
36-55	1,042.5	1,213.2	874.9
56-75	2,899.6	3,146.0	2,634.9
76+	5,302.1	5,709.5	4,658.1
Total	1,597.3	1,869.7	1,312.8
Total 18+	1,894.0	2,197.1	1,571.7

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197 In table 1 b, we present the prevalence rates in the year 2015 stratified by age and gender. The highest
 198 prescription rate was seen in the age group 76+ (5,302 persons per 100,000 insured persons in 2015).

199 In contrast, the prescription rate for minors was comparatively low (13.4 per 100,000 insured persons),

200 P/G was prescribed more frequently to women than to men (women: a total of 1,869.7 per 100,000

201 insured persons; men: a total of 1,312.8 per 100,000 insured persons).

202 Table 2 shows the annual incidence of P/G prescriptions from 2010-2015. As the prescription rate in
 203 general, the rate of new P/G prescriptions increased annually (Table 2).

Table 2: Annual incidence rates for new pregabalin/gabapentin prescriptions 2010-2015			
Year	Number of insured persons with new P/G prescriptions	Total Number of insured persons	Incidence per 100,000 insured persons
2010	22,776	3,701,696	615.3
2011	23,121	3,717,582	621.9
2012	24,750	3,977,347	622.3
2013	25,784	3,966,813	650.0
2014	27,613	3,952,306	698.7
2015	26,526	3,757,502	705.9
Mean value 2010-2015	25,095	3,845,541	652.4

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205 3.2. Areas of application

206 As mentioned earlier, P/G is approved for three applications: epilepsy, anxiety disorders, and
 207 neuropathic pain. However, our results show that the majority (77.9%) of P/G recipients had only
 208 received a diagnosis of pain but had suffered neither from epilepsy nor anxiety disorder (Table 3).

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Table 3: Diagnostic reasons for pregabalin/gabapentin prescriptions in 2015 (n=61,828)		
ICD diagnoses	Number of insured persons with P/G prescriptions	in per cent
Pain * (exclusive)	48,190	77.9
Epilepsy ** (exclusive)	793	1.3
Anxiety disorder *** (exclusive)	707	1.1
Pain + anxiety disorder	2,404	3.9
Pain + epilepsy	2,222	3.6
Pain + epilepsy + anxiety disorder	162	0.3
Epilepsy + anxiety disorder	49	0.1
No pain, epilepsy or anxiety disorder	7,198	11.6
* all ICD-10 pain diagnoses listed in the supplementary information		
** ICD codes: G40.- G41.-		
*** ICD codes: F41.1		

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211 In 11,6% of the cases, there was no evidence for any of the approved diagnoses for P/G prescription.
 212 P/G recipients who were diagnosed exclusively with epilepsy or anxiety (epilepsy: 1.3%; anxiety

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3 213 1.1%) were in the minority. Although the incidence of P/G prescriptions (excluding pain diagnoses)
4 214 have increased continuously over the years, the proportion of epilepsy and anxiety diagnoses remained
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6 215 relatively constant in the new P/G prescriptions group.
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9 217 **3.3. P/G application in pain patients**

11 218 After the number of patients with epilepsy were excluded, 25,251 insured persons with new P/G
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13 219 prescriptions remained. For these we determined the type of pain diagnoses. As presented in table 4, it
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15 220 appears that one quarter of all new P/G recipients (25.7% (line B+D+F+G)) were diagnosed with
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17 221 typical neuropathic pain.
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22 Table 4: **Pain-related diagnoses** in patients with new pregabalin/gabapentin prescriptions in 2015 (n=25,251)

Pain-related diagnoses		Number of insured persons	in per cent
A	1 Non-neuropathic pain (exclusive)	2,951	11.7
B	2 Typical neuropathic pain disorder (exclusive) (demonstrable benefit of a P/G therapy)	1,218	4.8
C	3 Pain with possible neuropathic or partial-neuropathic cause (exclusive) (no demonstrable benefit of P/G)	3,025	12.0
D	1 + 2	1,295	5.1
E	1 + 3	10,756	42.6
F	2 + 3	1,010	4.0
G	1 + 2 + 3	2,990	11.8
H	neither 1, 2 nor 3	2,006	7.9

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44 224 For the majority (70.4% (line C+E+F+G in table 4)) of new recipients, a neuropathic component was
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46 225 pathophysiologically conceivable, but there was no characteristic indication for P/G treatment. The
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48 226 three most frequent examples of this category were the diagnoses "M544_Lumboischialgia"
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50 227 (5,836/25,251), "M5416_Radiculopathy: Lumbar region" (4,978/25,251) and "M542_Cervical
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52 228 neuralgia" (4,543/25,251). In 19.6% of the cases (lines A+H in table 4), we found only a "non-
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54 229 neuropathic pain diagnosis" or "no pain diagnosis".

55 230 The percentage distribution of the pain-related diagnoses varied only marginally over time (typical
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57 231 neuropathic pain disorders: 17.8% (2011) - 18.6% (2013); Pain disorder with a neuropathic
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59 232 component: 72.4 (2011) - 73.8% (2013); non-neuropathic pain diagnosis/no pain diagnosis: 18.8%
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233 (2011) - 20.6% (2013).
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3 235 **3.4. Discontinuation of P/G treatment**
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5 236 As many as 85% (16,573/19,501) of insured persons who had received a new P/G prescription due to
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7 237 pain (excluding patients with epilepsy diagnosis) discontinued their treatment within the 2-year
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9 238 follow-up period. In the majority, discontinuation occurred within a short period. 61.1% of the patients
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11 239 did not receive a follow-up prescription (number of follow-up-prescriptions / figures in per cent:
12 240 1/13.2%; 2/7.5%; 3/5.4%; ≥ 4 /12.8%). In contrast, as few as 15% of the insured persons received
13 241 regular follow-up P/G prescriptions (2,928/19,501).
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4. Discussion

Our results reveal two contradictory trends: although the prescription figures for pregabalin and gabapentin increased annually in the investigation period, only about 25% of the patients with new P/G prescriptions showed a typical neuropathic pain disorder and a demonstrable benefit of a P/G therapy, in many cases resulting in discontinuation of this therapy.

These findings are in line with data from the United States of America ([8]).

Although the incidence of purely neuropathic pain disorders has been slightly increasing in the last years, the increase in the P/G prescription figures does not disproportionate. The steady rise of prescriptions indicates that P/G is being applied progressively in patients with "mixed chronic pain" (mixed pain). "Mixed pain" refers to chronic pain syndromes in which a mixture of nociceptive and neuropathic pain components is assumed [11, 12].

Regarding the pain diagnoses which are coded parallel to new P/G prescriptions, the question arises which chronic pain diagnoses should be classified as neuropathic or non-neuropathic. A clear differentiation between these two definitions does not exist. The S1-guideline "Diagnostics of neuropathic pain" (S1 level: expert group recommendation) [10] of the German Society of Neurology offers a broad catalogue of neuropathic pain diagnoses. Besides classical neuropathic pain syndromes (e.g. post herpetic neuralgia) where somatosensory nerve structures are damaged, the authors [10] also present pain diagnoses in which a neuropathic component is pathophysiologically conceivable (for example by nerve irritation in diagnosis like "lumboischialgia" or "radiculopathy") but do not necessarily comprise damaged nerve structures. Due to the fact that a differentiation is not therapeutically relevant [13]), we decided to differentiate the neuropathic pain diagnoses according to the proven benefit of P/G: "typical neuropathic pain disorder" with a demonstrable benefit of P/G therapy versus "pain, possibly with neuropathic or partially-neuropathic cause" with no evidence for the application of P/G.

Due to the nature of a routine data analysis, we were not able to determine the personal reasons for discontinuation. These possibilities include adverse effects or an absence of the desired pain-relieving effect. We assume that the high discontinuation rate reflects an ineffectiveness of P/G in chronic pain therapy.

The discrepancy between the high number of prescriptions and the discontinuation rate, potentially indicating a clinically unconvincing effect, raises the question why this drug might be so readily prescribed. Due to the complex nature of the doctor-patient-interaction, especially in the face of a chronic pain disorder, doctors might resort to second line medication to help their patients.

Furthermore, marketing strategies of the pharmaceutical industry [8], among others, that specifically target mixed-pain patients with neuropathic symptoms, may play an important role in their decision.

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5 280 Altogether, the results of this analysis suggest an overprescribing of P/G. In consequence, numerous
6 281 patients probably unnecessarily use medicine that is accompanied with polypharmacy risks (e.g. side
7 282 effects, drug-drug interactions). Furthermore, overprescribing is a high economic burden for the health
8 283 care system. For example, the costs for pregabalin has doubled from 2012 to \$4.4 billion in 2016 in
9 284 the United States [7, 8]. German data describe the same trends [3]. This might be a possibility for
10 285 savings for health insurance funds.
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16 287 However, secondary data analysis, which is based on accounting data on the utilisation of insured
17 288 persons from health insurance funds, can lead to systematic restrictions [14]. While the variable "P/G
18 289 consumption" can be considered a valid indicator (because P/G is only available on prescription), the
19 290 operationalisation of the pain-related diagnosis variables represents a challenge, because diagnosis
20 291 coding may happen insufficient. One possible reason are random errors that occur in the course of
21 292 diagnosis coding, resulting in a potential bias in both directions (diagnoses appear more or less severe
22 293 than in reality). Another reason may be the fact that doctors probably prefer to code clear neuropathic
23 294 diagnoses to justify the prescription even in cases where the neuropathic nature is unclear. This can
24 295 result in a lower proportion of evidence-based indications. On the other hand, misclassifications of
25 296 unspecific low back pain can produce an overestimation, since these diagnoses are often routinely
26 297 coded as "lumboischialgia" / "Radiculopathy: Lumbar region" or unspecific neck pain as "cervical
27 298 neuralgia".

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30 299 According to international literature, P/G is sometimes also used in off-label indications like hot flush,
31 300 restless leg, multiple sclerosis [15]. To avoid counting these cases erroneously as non-neuropathic pain
32 301 conditions, our methodological approach does not include off-label indications.
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42 303 Conclusion:

43 304 Our analysis leads to the assumption that the increasing use of pregabalin and gabapentin is not based
44 305 on the diagnosis of typical neuropathic pain conditions. Furthermore, high discontinuation rates
45 306 suggest that the anticipated therapeutic effect is lacking and/or adverse effects occur. Clinicians and
46 307 patients should exercise caution regarding pregabalin and gabapentin prescriptions.
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308 **5. Study protocol**

309 The study protocol is available on request. Please contact: annika.viniol@staff.uni-marburg.de.

310 **6. Funding**

311 This research received no specific grant from any funding agency in the public, commercial or not-for-
312 profit sectors.

313 **7. Competing interests**

314 The authors declare that they have no competing interests.

315 **9. Authors' contributions**

316 AV planned the study, discussed the results and wrote the manuscript. TP and LH analyzed data and
317 discussed the manuscript. KMK gave support to study design and discussed the manuscript. JW, JH,
318 NDB and AB discussed the results and the manuscript.

319 **10. Reporting statement**

320 Data analysis and reporting style is in accordance with the “German Reporting Standard for Secondary
321 Data Analyses” (STROSA).

322 **11. Patient consent**

323 Due to the nature of secondary data analysis, no patient consent is required.

324 **12. Data sharing statement**

325 Data used in the analyses are entrusted in the Institute for Applied Health Research Berlin. Please
326 contact: jochen.walker@hrisk.de

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The classification criteria of the pain-related diagnosis

ICD-10 pain code “not neuropathic”

F413	fear/tension- type pain syndrome
F4534	psychogenic painful micturition
F4539	psychogenic pain of the abdomen
F4540	continuing somatoform disorder
F4541	chronic pain with somatic and psychological factors
G440	cluster headache
G441	vasomotor headache
G442	tension headache
G443	chronic posttraumatic headache
G444	headache caused by drugs
G448	other headache without detailed specification
G501	atypical facial pain
H571	eye pain
I702	arteriosclerosis of the extremities: physical stress induced leg pain
L905	cicatix pain
M2550	joint pain: multiple sites
M2551	joint pain: shoulder region (clavicula, scapula, acromioclavicular-/shoulder-/sternoclavicular joints)
M2552	joint pain: upper arm (humerus, elbow joint)
M2553	joint pain: forearm (radius, ulna, wrist)
M2554	joint pain: hand (finger, carpus, metacarpus)
M2555	joint pain: pelvic region and thigh (pelvis, femur, buttocks, hip, hip joint, sacroiliac joint)
M2556	joint pain: lower leg (fibula, tibia, knee joint)
M2557	joint pain: ankle and foot (tarsal, metatarsal, toes, ankle, subtalar joint, other ankle joints)
M2558	joint pain: multiple sites (neck, head, ribs, torso, spine)
M2559	joint pain: multiple localisation
M545	back pain
M546	pain in area of thoracic spine
M5480	other back pain: different areas of the spine
M5481	other back pain: atlanto-occipital joint
M5482	other back pain: cervical area
M5483	other back pain: cervical-thoracic area
M5484	other back pain: thoracic area
M5485	other back pain: thoracic-lumbar area
M5486	other back pain: lumbar area
M5487	other back pain: lumbar-sacral area
M5488	other back pain: sacral area
M5489	other back pain: not detailed localisation
M5490	back pain- nondetailed specification: several localisations of the spine
M5491	back pain- no detailed specification: atlanto-occipital joint
M5492	back pain- no detailed specification: cervical area
M5493	back pain- no detailed specification: cervical-thoracic area
M5494	back pain- no detailed specification: thoracic area
M5495	back pain- no detailed specification: thoracic-lumbar area
M5496	back pain- no detailed specification: lumbar area
M5497	back pain- no detailed specification: lumbar-sacral area
M5498	ankle and foot (tarsal, metatarsal, toes, ankle, subtalar joint, other ankle joints)
M5499	back pain- not detailed specification: area not detailed localisation
M7960	pain in extremities: several localisations
M7961	pain in extremities: shoulder region (clavicula, scapula, acromioclavicular-/shoulder-/sternoclavicular joint)
M7962	pain in extremities: upper arm (humerus, elbow joint)
M7963	pain in extremities: forearm (radius, ulna, wrist)
M7964	pain in extremities: hand (finger, carpus, metacarpus)
M7965	pain in extremities: pelvic region and thigh (pelvis, femur, buttocks, hip, hip joint, sacroiliac joint)
M7966	pain in extremities: lower leg (fibula, tibia, knee joint)
M7967	pain in extremities: ankle and foot (tarsal, metatarsal, toes, ankle, subtalar joint, other ankle joints)
M7969	pain in extremities: no detailed localisation
M961	post dissection syndrome
N3981	flank pain
N940	intermenstrual pain
O294	headache after spinal cord anesthesia during pregnancy
O745	headache after spinal cord anesthesia during pregnancy
O894	headache after spinal cord anesthesia during childbirth
R070	sore throat

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4	R072 precordial pain
5	R073 other kind of chest pain
6	R074 chest pain: no detailed specification
7	R101 pain in the area of upper abdomen
8	R102 pain in the area of pelvis and perineum
9	R103 pain in other areas of lower abdomen
10	R104 other pains without detailed specification
11	R309 pains passing water without detailed specification
12	R51 headache
13	R520 acute pain
14	R521 chronic unswayable pain
15	R522 other chronic pain
16	R529 pain without detailed specification
17	
18	ICD-10 pain codes “typically neuropathic”
19	(Diagnoses with an improved evidence via controlled randomised studies)
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21	B02 herpes zoster
22	G500 trigeminal neuralgia
23	G530 post zoster neuralgia
24	G546 phantom pain
25	G9585 deafferentation pain due to spinal cord impairment
26	M797 fibromyalgia
27	T926 stump pain after traumatically arm amputation
28	T936 stump pain after traumatically leg amputation
29	
30	ICD-10 pain code “possibly neuropathic”
31	(diseases with a potentially neuropathic genesis based upon aetiology/anatomical deliberations,
32	independent from the therapeutic benefit of P/G according to the guideline “diagnostic for neuropathic
33	pain” from the German Society of Neurology [1])
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35	G130 paraneoplastic neuromyopathy and neuropathy
36	G521 diseases of N. glossopharyngeus and glossopharyngeus neuralgia
37	G56 mono neuropathy of the upper extremity
38	G57 mono neuropathy of the lower extremity
39	G58 other mono neuropathies
40	G59 mono neuropathy parallel to other illness
41	G60 hereditary and idiopathic neuropathy
42	G61 polyneuritis
43	G62 other polyneuropathies
44	G63 polyneuropathy parallel to other illness
45	G990 autonomous neuropathy through endokrinal and metabolic diseases
46	M501 cervical intervertebral disc degeneration with radiculopathy
47	M511 lumbal intervertebral disc degeneration with radiculopathy
48	M541 radiculopathy
49	M542 cervical neuralgia
50	M543 ischialgia
51	M544 lumboischialgia
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1 Deutsche Gesellschaft für Neurologie. Diagnostik neuropathischer Schmerzen: S1-Leitlinie 2012.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5-8
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	Cross sectional study
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-8
Bias	9	Describe any efforts to address potential sources of bias	5-8
Study size	10	Explain how the study size was arrived at	Secondary data analysis
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Cross sectional study
		(b) Describe any methods used to examine subgroups and interactions	5-8
		(c) Explain how missing data were addressed	5-8
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	5-8

		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	Cross sectional study
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-11
		(b) Give reasons for non-participation at each stage	Secondary data analysis
		(c) Consider use of a flow diagram	Secondary data analysis
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	9-11
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Cross sectional study
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	Cross sectional study
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	Cross sectional study
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	9-11
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Cross sectional study
		(b) Report category boundaries when continuous variables were categorized	9-11
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Cross sectional study
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13-14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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4 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE
5 checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
6 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.
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